CUK-H06050-30-P25394

Volume 99, Number 1, January 1992

BJOGAS 99(1) 1–88 1992 ISSN 0306-5456

UCA

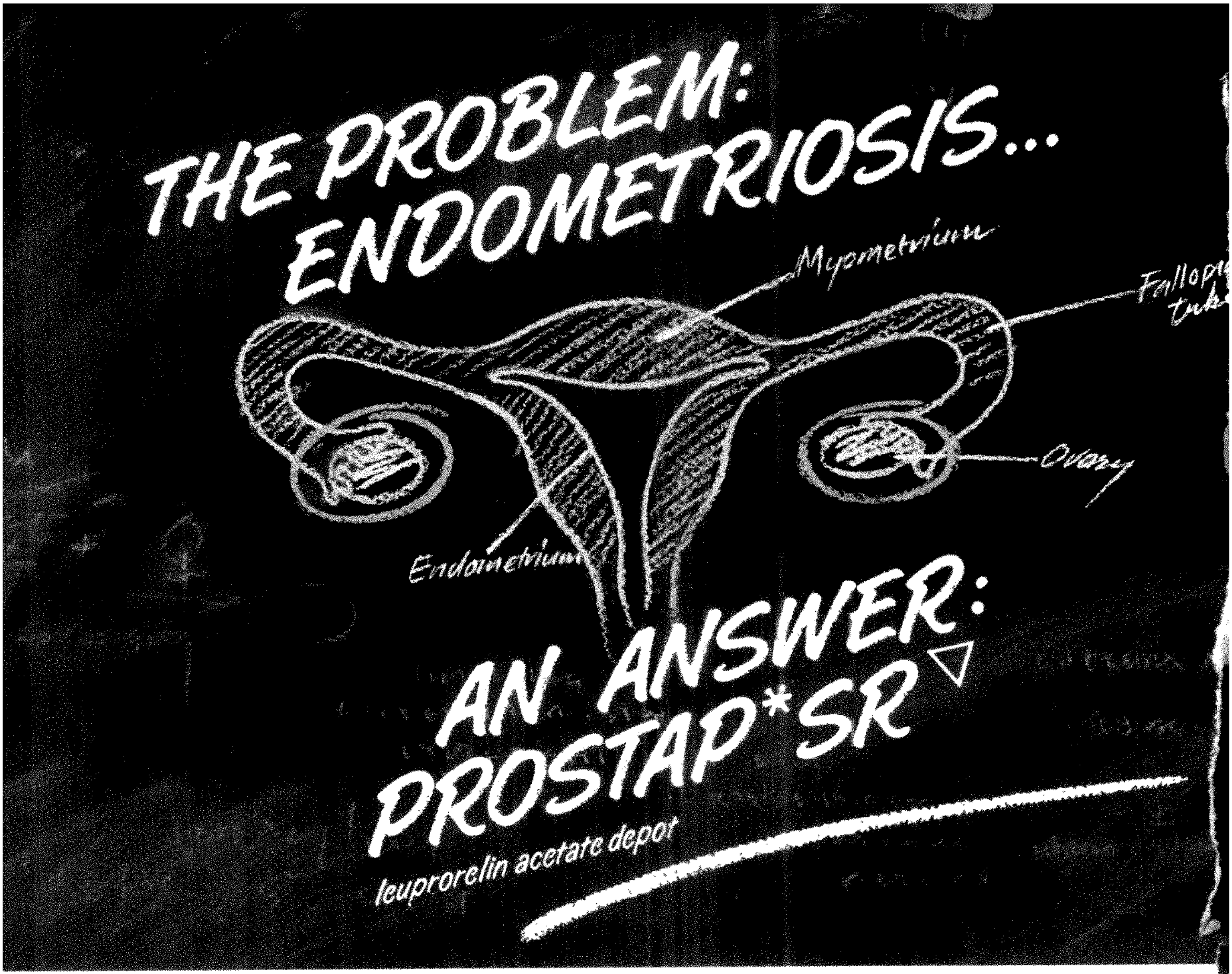
British Journal of Obstetrics and Gynaecology

30

Edited by David B. Paintin

SUPER ARDUA

Published on behalf of the
Royal College of Obstetricians and Gynaecologists
by Blackwell Scientific Publications



Effective GnRH agonist therapy for endometriosis,[1,2] from a simple monthly subcutaneous injection.

A very fine suspension, given through a fine gauge needle, offers patient acceptability and ease of administration in clinic, outpatient or domiciliary use.

P 25,394

PROSTAP* SR▼

leuprorelin acetate depot

A Logical Approach to Endometriosis

REFERENCES

1. Dlugi AM *et al* Fertility & Sterility 1990; **54** (3) 419-427. (RJG33) **2.** Adashi E *et al* Data on File Lederle Laboratories.

ABBREVIATED PRESCRIBING INFORMATION Before prescribing Prostap SR, please refer to full data sheet **Presentation:** Vials containing 3.75mg leuprorelin acetate as microcapsule powder. For reconstitution with Sterile Vehicle, presented in a prefilled syringe. **Indications:** Th management of endometriosis, including pain relief and reduction of endometriotic lesions **Dosage:** 3.75mg administered as a single subcutaneous or intramuscular injectio month for a maximum period of 6 months. Treatment should be initiated during the first 5 days of the menstrual cycle. **Contraindications:** Lactation, pregnancy, undiagnose abnormal vaginal bleeding **Warnings:** Whilst ovulation is usually inhibited during therapy, contraception is not ensured, therefore, patients should use non-hormonal meth contraception. During the early phase of therapy, sex steroids temporarily rise, possibly leading to an increase in symptoms. This, however, dissipates with continued therapy **Precautions, side-effects:** The induced hypo-oestrogenic state results in a small loss in bone density over the course of treatment, some of which may not be reversible. How during one six-month treatment period, this bone loss should not be important. The generally accepted level of bone loss with LHRH analogues such as Prostap is 5%. For pat with major risk factors for decreased bone mineral content, Prostap therapy may pose an additional risk. Other side effects reported are mainly those related to hypo-oestroge hot flushes, headaches, emotional lability, and vaginal dryness. **Legal category:** POM **Package Quantities:** Vials containing 3.75mg leuprorelin acetate as microcapsule pow Prefilled syringes containing 2ml of sterile vehicle. **Basic NHS cost:** £125.40. **Product Licence Numbers:** Prostap SR Powder 3.75mg vials, PL0095/0218. Sterile vehicle pref syringes PL0095/0220 Cyanamid of Great Britain.

For further information, see data sheet.
Lederle Laboratories, Fareham Road, Gosport, Hants PO13 0AS.

Lederle Takeda

***Trademark of Takeda**
***Under licence of Takeda Chemical Industries Ltd, Japan.**

British Journal of Obstetrics and Gynaecology

Editor: David B. Paintin

Editorial Advisers: F. E. Hytten *London*, I. Chalmers *Oxford*

Assistant editors: Sheila L. B. Duncan *Sheffield*, R. P. Husemeyer *Grantham*

Editorial assistants: Sonja Chayen, Valerie Bolton, Jayne Marchant

Statistical advisers: D. G. Altman *London*, Diana Elbourne *Oxford*, Helen Tate *Saffron Walden*

Editorial board
C.H. Buckley *Manchester*
R.W.I. Cooke *Liverpool*
J.O. Drife *Leeds*
I.D. Duncan *Dundee*
S. Franks *London*
R.B. Fraser *Sheffield*
J.M. Grant *Bellshill*
J.M. McGarry *Barnstaple*
J.P. Neilson *Edinburgh*
R.S. Sawers *Birmingham*
G.E. Smart *Edinburgh*
P.J. Steer *London*
J.W.W. Studd *London*
M. de Swiet *London*
D.W. Warrell *Manchester*

British Journal of Obstetrics and Gynaecology is published on behalf of the Royal College of Obstetricians and Gynaecologists by Blackwell Scientific Publications. The *Journal* publishes reports of original work in obstetrics and gynaecology and related subjects such as human reproductive physiology and contraception; articles reviewing topics in these fields are also acceptable. A section for brief communications, including case reports, allows more rapid publication of papers of not more than 600 words. *British Journal of Obstetrics and Gynaecology* is covered in *Current Contents, ISI/BIOMED, Science Citation Index, Index Medicus, CABS*, and the ADONIS service, whereby copies of individual articles can be printed out from compact disks (CD-ROM) on demand. An explanatory leaflet is available from the publisher.

Books for review

Books for review should be sent to the *British Journal of Obstetrics and Gynaecology*, 27 Sussex Place, Regent's Park, London NW1 4RG.

Correspondence

Letters should be sent to The Editor, *British Journal of Obstetrics and Gynaecology*, 27 Sussex Place, Regent's Park, London NW1 4RG.

As the space available for correspondence is limited, only a selection of letters submitted will be printed. Letters should be brief, factual and related to original work recently published in the *Journal*. The editorial staff reserve the right to shorten letters and make minor corrections. Letters may be published together with a reply from the original author.

Subscription information

The *British Journal of Obstetrics and Gynaecology* is published monthly and annual subscriptions for 1992, accepted on a calendar year basis only, are £90.00 (UK), $165.00 (USA and Canada) and £95.00 (elsewhere), post free. Fellows, Members and successful Part 1 candidates of the Royal College of Obstetricians and Gynaecologists are entitled to subscribe at the special price of £29.00 (UK), £39.00 elsewhere and $68.00, USA and Canada (add $4.76 GST in Canada), also post free. Orders for current subscriptions and back issues should be sent to Blackwell Scientific Publications Ltd, PO Box 88, Oxford OX2 0NE; all other business correspondence, including orders for offprints and advertising space, should be addressed to Blackwell Scientific Publications Ltd, Osney Mead, Oxford OX2 0EL (telephone no. 0865 240201, telex 83355 Medbok G, fax 0865 721205).

Dispatch

The *Journal* is dispatched within Europe by surface mail, to other continents by various forms of air speeded delivery: to the US* by air freight for forwarding by second class post, to India by air freight for guaranteed local delivery, and to all other countries by Accelerated Surface Post.

Copyright and photocopying

Articles published in the *Journal* become its copyright. Reproduction elsewhere, in whole or in part, is not permitted without the previous written consent of the author and editor, and the customary acknowledgments must be made.

© 1992 Blackwell Scientific Publications Ltd. Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by Blackwell Scientific Publications Ltd for libraries and other users registered with the Copyright Clearance Center (CCC) Transactional Reporting Service, provided that the base fee of $06.00 per copy is paid directly to CCC, 27 Congress Street, Salem, MA 01970, USA. 0306-5456/92 $06.00.

This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale. Special requests should be sent to the Editor.

Business correspondence

Orders and remittances relating to subscriptions, back numbers and offprints should be sent to Blackwell Scientific Publications, PO Box 88, Oxford.

Advertisements

Advertisement bookings and enquiries should be sent to the Advertisement Manager, Blackwell Scientific Publications, Osney Mead, Oxford OX2 0EL (Telephone 0865 240201, Fax 0865 721205).

This journal is printed on acid-free paper.

---

* *Postmaster, send address changes to* British Journal of Obstetrics and Gynaecology, *c/o Mercury Airfreight International Ltd., 2323 EF Randolph Avenue, Avenal NJ07001 (US Mailing Agent). Second Class Postage Paid at Rahway NJ.*

Directions to contributors

All papers should be sent to The Editor, *British Journal of Obstetrics and Gynaecology*, 27 Sussex Place, Regent's Park, London NW1 4RG. Papers received and the data they contain are assumed to have been submitted exclusively to the *British Journal of Obstetrics and Gynaecology* and *all* authors must give signed consent to publication in a letter sent with the manuscript. The Editor will decide on the time of publication and retains the usual right to modify the style and length of a contribution, major changes will be agreed with the author(s).

Peer review

Manuscripts are subjected to peer review in relation to both the scientific and the statistical content As far as possible the scientific referees are unaware of the authorship and the department of origin and the work The peer review process takes a minimum of six weeks Papers that are accepted are published about four to five months later

Presentation of manuscripts

Three copies of the manuscript and illustrations should be sent. Manuscripts should be typed double spaced on one side of the paper, with wide margins. To facilitate blind refereeing, the names of the author(s), their appointment(s) and their department(s) should be given on a separate front sheet and any acknowledgments on a separate back sheet. As far as possible, authors should avoid identifying themselves or their department in the text, but such identification is inevitable in some types of paper. When papers have been accepted for publication, and after any revision has been completed, authors are encouraged to submit the final version on disk. This should be IBM compatible. An accurate hard copy must accompany each disk, together with details of the type of computer used, the wordprocessing software and the disk operating system. The text must not be justified Particular attention should be taken that the final version adheres to the style of the journal in all respects. Further details can be obtained from the publishers. Authors are advised to keep a copy of all manuscripts, as no responsibility can be accepted for loss.

Reports of original work should usually be arranged in the conventional order of abstract, introduction, methods, results, discussion, acknowledgments and references, with suitable headings for each part. Two further sub-divisions, with appropriately less significant headings, can be used, the third order heading runs on with text at a paragraph opening. Results may be presented in the text, in tables and/or figures, but the text should, in general, comment on rather than repeat information in tables Abstracts are structured and use an appropriate selection of the headings· Objective; Design; Setting; Subjects; Interventions; Main outcome measures; Results; Conclusions. Abstracts should not exceed 250 words

Case reports and short communications do not require a summary or introduction Short communications should not exceed 600 words and contain no more than one table or figure.

Letters to the editor are published only if they comment usefully on material published in previous issues. Letters should not exceed 400 words and must be typed with double line-spacing.

Tables and figures

Tables and figures should be separate from the text, with their positions indicated in the text margin Both are numbered with arabic numerals. Coloured illustrations are used sparingly when these appreciably improve clarity

Figures should be marked on the back (lightly in pencil) only with the name of the paper, the figure number and to indicate the top. Each should have a descriptive legend typed on a sheet separate from the figure. Photographs should be unmounted glossy bromide prints of good contrast.

Figures consist of all material which cannot be set in type, such as photographs, line drawings, etc Tables are not included in this classification and should not be submitted as photographs Original X-ray films should not be sent—glossy prints must be submitted.

Line drawings should be on white board, arranged to conserve space, and should allow for reduction to 81 mm (single column) or 170 mm (double column). Computer-generated graphics should be printed on good quality plain white paper. The layout should be as simple as possible—three-dimensional effects should be used only if this is necessary to express a third variable.

Typewritten lettering should not be used on illustrations and explanations should appear in the legend not on the figure itself.

Unless written permission for publication from the patient, or the parent or guardian is submitted, the identity of patients in illustrations should be completely concealed by restricting the field to the area of interest or by obscuring the face

Units and abbreviations

Measurements should be expressed in SI units with the exception of haemoglobin (g/dl) and blood pressure (mmHg). If the original observations were recorded in other units this should be stated, together with the appropriate conversion factors. Standard abbreviations, without punctuation, are used. *Units, Symbols and Abbreviations* (1988) published by the Royal Society of Medicine provides a useful guide. Abbreviations are used sparingly and only if a lengthy name or expression is repeated frequently throughout the manuscript. Words must appear in full on first appearance in both abstract and text, followed by the abbreviation in parenthesis

Drugs are described by their official names but trade names should be indicated in brackets the first time a drug is quoted in the main text.

Statistics

Authors should describe clearly the design of their investigation and the source of the data. All statistical methods should be specified so that it is clear which was used where. Papers omitting this information may be returned without review. The basic principle to follow is to supply sufficient information about the design and methods of analysis to allow the research to be repeated by someone else

The journal has published check lists to guide contributors preparing accounts of certain types of research These appeared in 1989 (Vol **96**): Bracken M. B , Reporting observational studies, 383–388; Wald N. & Cuckle H., Reporting the assessment of screening and diagnostic tests, 389–396; Grant A., Reporting controlled trials, 397–400

Some points of detail to note are:

(1) It is not acceptable to present the results of a statistical analysis solely by a *P* value—actual results such as means or proportions should always be given, along with the test statistic.
(2) The use of confidence intervals is encouraged.
(3) The symbol ± should not be used when presenting SE or SD. Presentation such as 'the mean . . . was 14 2 (SD 3 2) mg' is preferred.
(4) When paired comparisons are made it is desirable to indicate the variability of within-pair differences.
(5) Unusual methods of analysis should be described and/or referenced.

Authors are referred to the general statistical guidelines of Altman *et al* (1983) for advice about the presentation and interpretation of the statistical aspects of their research.

Altman, D. G., Gore, S. M , Gardner, M. J. & Pocock, S. J. (1983) Statistical guidelines for contributors to medical journals. *Br Med J* **286**, 1489–1493.

Human experiments

Manuscripts should contain a statement that the work was approved by the ethics committee of the institution in which it was done and that subjects gave informed consent to the work. The editors reserve the right to reject papers if they consider the ethical justification to be questionable.

References

In the text, use the name of the author(s) followed by their date of publication; where there are two authors use the form: Smith & Brown 1972; where there are more than two authors use Robinson *et al.* 1979.

Arrange the list of authors quoted at the end of the text in alphabetical order set out as follows.

Name(s) and initials of all author(s), year of publication (in brackets), title of the article, name of the journal (abbreviated according to *Index Medicus*), volume number, first and last page numbers In the case of books the order is: Name(s) and initials of author(s), year of publication (in brackets), full title, edition, publisher and place of publisher, page numbers. Where appropriate, the chapter title and the names of the editors should be given.

References to 'personal communications' and 'unpublished work' may be quoted in the text but should not be included in the references Examples of the style to be used are given below:

Trudinger B. J., Lewis P. J. & Petit B. (1979) Fetal breathing in intrauterine growth retardation. *Br J Obstet Gynaecol* **86**, 432–436

Hytten F. E. & Leitch I (1971) *The Physiology of Human Pregnancy* 2nd edn, Blackwell Scientific Publications, Oxford, p 26.

Proofs and offprints

Manuscripts should specify the name and address of the author to whom correspondence and page proofs should be sent Only essential corrections can be accepted, more extensive alterations, which may delay publication, will be charged to the author. Fifty offprints of each paper are supplied free, but additional copies may be ordered on the printed sheet sent with the proofs.

British Journal of Obstetrics and Gynaecology
January 1992, Vol. 99, pp. 1–4

COMMENTARIES

The British Journal of Obstetrics and Gynaecology—1992

The Journal has a new look and we hope you like it. The larger pages contain more words but, more importantly, provide more flexibility for tables and illustrations. The contents have been classified into sections and these will appear in the same order in each issue to help readers find the articles in which they have a particular interest. Advertisers prefer the larger format and we hope to increase our income from this source. The larger size will necessitate some reorganization of library shelves and we apologise for the inconvenience this will cause.

The Journal will continue to publish accounts of clinical research that have passed the peer-review process and will endeavour to maintain its position as one of the world's leading publications in our speciality. There will be commentaries on topics of current importance. More educational reviews will appear and, in the course of 1992, there will be several supplements—at no additional cost to subscribers.

The introduction of the new format coincides with a marked reduction in the cost of a subscription to Fellows and Members and successful Part 1 candidates of the Royal College of Obstetricians and Gynaecologists. A personal copy will keep readers in touch with clinical research not only in the United Kingdom but in Europe and the Commonwealth and will be an important component in personal postgraduate education.

David B. Paintin
Editor

British Journal of Obstetrics and Gynaecology
January 1992, Vol. 99, pp. 1–3

Prognosis of surviving very low birthweight infants: still in the dark

'Will my baby be all right?'

The question makes us feel uncomfortable. We fumble for answers, stammer statistics, but the question is restated: 'Yes, doctor, but will my baby be all right?' There was a time, which now seems antediluvian, when the answer was a simple 'yes, the baby will live', or 'No, the baby will die'. Our discomfort is increased because parents tend to ask this particular question at night (the hospital may be well lit, but we know—our tired bodies remind us, should there be any doubt—that it is after dark).

What can we tell the parents of a very low birthweight (<1500 g) infant about their child's prognosis? One thing is certain: chances are the child will be discharged from the hospital alive. Of this the statistics leave no doubt: 74% of babies weighing less than 1500 g at birth survive to hospital discharge; among those weighing 1251–1500 g survival ranges from 89 to 98% (Hack *et al.* 1991). But that does not dispel the darkness, for the question can be put differently: Will my child be handicapped? Will my child have cerebral palsy? Answers to these questions are less certain.

We turn to the literature, to multiple 'outcome studies' describing the fate of those immature infants that have survived. When one first confronts such studies—usually as citations in review articles—one has the impression that definite answers can be given: so and so says x% of babies under 1500 g are 'entirely normal'. If one looks a little harder, this impression is replaced by one of confusion: there seem to be so many of these studies, reporting all sorts of numbers, that no answer seems possible at all.

In an attempt to address these questions, my colleagues and I performed a structured review of the very low birthweight infant outcome literature and studied the fate of very low birthweight survivors born since 1960 (Escobar *et al.* 1991). There are now some answers we can give parents—and a lot of questions we can ask ourselves as doctors.

After examining 1136 English language references, we discovered that the apparent profusion of outcome studies is deceptive: we could only identify 111 studies that examined *all* very low birthweight infants born at a specific locale (hospital or geographic region) during a defined period of time, that is, cohorts that did not exclude infants in a non-random fashion. This may seem like a lot of studies—the total number of births was 26 099—but closer inspection revealed that only 7000 or so infants were actually followed for more than 12 months.

This means that, since 1960, on the average, only about 250 such infants were followed annually. Every year there are approximately 6000 very low birthweight births in England (Pharoah & Alberman 1988 and 1990); the number born in the United States is between 35 000 and 40 000 per year (Office of Technology Assessment 1987).

'x% were entirely normal.' One must immediately ask: x% of what? What is the denominator? Rates of any outcome vary dramatically depending on what denominator one employs (Kitchen & Murton 1985). Among the outcome studies we reviewed we identified 19 different denominators, including livebirths, admissions to the nursery within 24, 48, 72 and 96 h after birth, survivors at 36 h, and survivors at discharge. Lost admidst the *P*-values, *f*-statistics, and confidence intervals is an elementary principle: the answer depends a lot on the number beneath the numerator. Only 23% of the studies we examined reported the number of livebirths.

Each denominator has a different application. Using livebirths as the denominator is desirable if one wishes to compare mortality with governmental vital statistics. On the day the very low birthweight infant is born, the parents will want to know percent survival using this denominator. Their questions will change when they go home—chances are they will be more interested in knowing what proportion of hospital survivors will have cerebral palsy. A nursery director wishing to assess his staff's abilities with resuscitation in the delivery room would want to know survival among inborn infants not having lethal anomalies, while a regional planner overseeing a group of nurseries would have different needs. Consideration of this issue leads us to an important conclusion: outcome studies must state their purpose clearly and, as much as possible, should consider the relevance of their results to those who will actually care for hospital survivors.

Seen from a parent's perspective, what is *not* reported in these papers is even more distressing: not all studies report rates of cerebral palsy, blindness, deafness, and sudden infant death. Shockingly, many conditions that would devastate families, cerebral palsy, for example, are not considered handicaps or are listed as 'minor'.

Nonetheless, despite these important methodological concerns, certain inferences can be made. The most solid of these concerns cerebral palsy. No time trend exists and, among infants followed to at least one year of age, the median cerebral palsy rate among the 85 cohorts we identified was 7·7% (CI 5·3–9·0), 38 times the frequency in the general population, which is about 2 per 1000 livebirths (Stanley & Blair 1991). Not content with our own estimate, we compared it to other studies, such as those reported by Stanley & Watson (1988), Hagberg *et al.* (1984 and 1989), the National Collaborative Perinatal Project (Ellenberg & Nelson 1979), and found them to be in the same range. Since the rate of cerebral palsy is (at the very least) remaining constant as survival increases, it is inevitable that the absolute number of children, and adults (Evans *et al* 1990), with cerebral palsy will increase.

What about disability rates? The median disability rate among the 106 cohorts that made some judgement on this outcome was 25·0% (CI 20·9–30·0) of infants followed to at least one year of age. Our estimates here are on less solid ground because there is no agreement as to what constitutes an adverse outcome in these infants. Examination of the methodology, which showed that many studies did not report certain adverse outcomes, supports the suspicion that the literature might underestimate morbidity. Judgments as to time trends are equally hazardous because of the tremendous variation in the enrolment periods, which ranged from 8 months to 16 years. Unlike the situation with cerebral palsy, we could not confirm or refute our estimate. No other sources of information on disability rates in very low birthweight infants exist.

Certain subgroup analyses we performed gave us surprising results that only future studies can confirm or refute. Centres handling higher volumes had higher cerebral palsy rates: does this reflect referral bias? Such centres also had lower disability rates: does this reflect better outcomes thanks to more experienced caregivers? Studies that made *any* attempt at quantifying socioeconomic status reported higher disability rates: does this mean that the more one looks, the more one finds?

Studies following infants for longer periods reported higher disability rates. What one can tell the parents of an immature infant will thus depend on how old the child is, and the validity of statements will vary with the degree of attrition due to deaths in liveborn cohorts. Hence the importance of agreement not only on denominators, but on the time definitions of such denominators.

Most surprising to us was that studies from the United States reported higher rates of disability, 30·0% *vs* 20·5% for non-United States studies. One could argue endlessly about the correctness of these estimates, but only one thing is certain: insufficient data are available, and no amount of data can resolve the issues until people agree on uniform denominators, time definitions, and outcome measures.

Clinicians would like to know the extent to which obstetric and neonatal variables, e.g. fetal growth retardation, birthweight, use of mechanical ventilation or intraparenchymal haemorrhage, modify outcome in very low birthweight infants. We found that the literature cannot answer such questions because studies do not consistently report outcome in subsets of infants. We were thus unable to assess the impact of factors such as being small for gestational age or being subjected to inter-hospital transport. This was true even with such a discrete variable as birthweight—few studies provided information on the distribution of deaths or losses to follow-up across different weight ranges. For example, 53 of the 106 cohorts reporting disability rates did not permit a breakdown between infants weighing 500–999 g and 1000–1499 g. Not surprisingly, our subgroup analyses failed to detect differences in rates of cerebral palsy and disability between heavier and lighter very low birthweight infants

Some might say that all this does not matter anyway, because one cannot predict the fate of an individual baby. But empiric data exist suggesting that harder numbers would be welcomed by parents: a study on the coordination of care of children with chronic illnesses found that physicians underestimated parental need for information about their child's diagnosis and prognosis (Liptak & Revell 1989).

So, hazy outlines with respect to certain outcomes begin to be discerned, but we remain largely in the dark. The parents' questions continue. Perhaps we could ask ourselves another one: are studies that single out institutions and caretakers the best way to ascertain outcome? Would it not be better to create incentives for cooperative studies that employ uniform outcome measures and pay closer attention to methodology?

One promising approach was suggested to me by a Spanish neonatologist, Dr Jose Arizcún. He convinced all the intensive and intermediate care nursery directors in the province of Madrid to agree to a common, 50-item 'minimum neonatal data-set'. Nurseries are free to collect whatever other data they might desire, but they must be able to provide the 50 items, a sort of outcome Esperanto. Coupled with the use of standardized definitions and common denominators (livebirths at each facility and livebirths born to residents of Madrid) such a data-set will permit valid inter-nursery comparisons.

Could we not do the same for outcome studies for high risk infants? One can envisage such a minimum data-set: livebirths as the denominator, a common definition for cerebral palsy (Evans *et al* 1986), two or three standardized tests, masked evaluators, random sampling. Then, at the very least, we could be certain our studies were comparable: a very good start toward dispelling some of the darkness.

Gabriel J. Escobar
The Permanente Medical Group
Division of Research
3451 Piedmont Avenue
Oakland, California 94611

References

Ellenberg J. H. & Nelson K. B. (1979) Birthweight and gestational age in children with cerebral palsy or seizure disorders. *Am J Dis Child* **133,** 1044–1048.

Escobar G. J., Littenberg B. & Petitti D. B. (1991) Outcome among surviving very low birthweight infants: a meta-analysis *Arch Dis Child* **66,** 204–211.

Evans P., Johnson A., Mutch L. & Alberman E. (1986) Report of a meeting on the standardization of the recording and reporting of cerebral palsy. *Dev Med Child Neurol* **28,** 543–549.

Evans P M , Evans S. J. W. & Alberman E (1990) Cerebral palsy: why we must plan for survival. *Arch Dis Child* **65,** 1329–1333

Hack M., Horbar J D., Malloy M. H., Tyson J E., Wright E. & Wright L (1991) Very low birthweight outcomes of the National Institute of Child Health and Human Development neonatal network *Pediatrics* **87,** 587–597.

Hagberg B , Hagberg A. & Olow I. (1984) The changing panorama of cerebral palsy in Sweden. IV. Epidemiological trends 1959–78. *Acta Paediatr Scand* **73,** 433–440.

Hagberg B., Hagberg A., Olow I. & Von Wendt L. (1989) The changing panorama of cerebral palsy in Sweden. V. The birth year period 1979–82. *Acta Paediatr Scand* **78,** 283–290.

Kitchen W. H. & Murton L. J. (1985) Survival rates of infants with birthweight between 501 and 1000 g. Improvement by excluding certain categories of cases. *Am J Dis Child* **139,** 470–471.

Liptak G. S. & Revell G. M. (1989) Community physician's role in case management of children with chronic illnesses. *Pediatrics* **84,** 465–471.

Office of Technology Assessment (1987) *Neonatal Intensive Care for Low Birthweight Infants: Costs and Effectiveness.* Health Technology Case Study 38. Washington D.C.: US Government Printing Office.

Pharoah P. O D. & Alberman E. (1988) Annual statistical review. *Arch Dis Child* **63,** 1511–1515.

Pharoah P. O. D & Alberman E (1990) Annual statistical review. *Arch Dis Child* **65,** 147–151.

Stanley F. J. & Watson L. (1988) The cerebral palsies in Western Australia: Trends, 1968 to 1981. *Am J Obstet Gynecol* **158,** 89–93.

Stanley F J. & Blair E. (1991) Why have we failed to reduce the frequency of cerebral palsy? *Med J Aust* **154,** 623–626.

British Journal of Obstetrics and Gynaecology
January 1992, Vol. 99, pp. 3–4

MD madness

The United Kingdom is virtually alone in encouraging a second post-graduate qualification before becoming a consultant, or even a senior registrar, in obstetrics and gynaecology. The irrelevance of the FRCS diploma has been debated in these columns (Studd 1983; Cameron 1984) and this view, together with the introduction of more demanding requirements by the Royal College of Surgeons, have now discouraged trainees from pursuing this path. It is good that subsequently there has been a greater emphasis on the clinical research which is essential for the development of new clinical skills but have we merely exchanged one obstacle for another—the MD?

An important personal view (Pinion 1991) from a skilled FRCS/MRCOG after years of hard clinical labour revealed a failure even to be shortlisted for many senior registrar jobs; the candidates interviewed all holding the MD in addition to the MRCOG. This, together with numerous examples known to us all, suggests a considerable defect in training, and unfairness in the process of selection for promotion. It is probable that this Gadarene stampede for a research degree has been counter-productive.

An MD is now seen as the fast lane to success. The trainee who emerges from a 'paper factory' without comprehensive clinical skills but being supported more by the research reputation of his supervisor than by his own ability is more likely to be appointed to a senior registrar or consultant post than the trainee with more extensive clinical experience and vocational motivation to treat his/her patients well. Such is the price of abandoning the FRCS without creating an alternative period of relevant clinical research or sub-specialty training.

What does an MD mean? Is it merely a piece of shorthand for committee members who have not made themselves aware of the candidate's original work? Is it necessary for a teaching hospital post, a district general hospital consultancy or an academic position? Three of the four NHS consultants in one

London teaching hospital have an MD but only one of the five academics, with their undoubted clinical skills and international research reputations, has felt it necessary to submit such a thesis. This in no way impugns their ability but the only conclusion to be made is that this most academic of degrees does not separate the academics from the rest. It may (but usually does not) select those who subsequently distinguish themselves in hospital research but certainly does not indicate competence for the hard clinical slog of a district hospital. A case can be made for a formal presentation of a thesis for those whose ultimate goal is a senior lectureship or a chair. Perhaps an MD should be evidence of formal training in clinical research and should be considered only for academic appointments. But, at the moment an MD is often merely a device to occupy 2–3 years of a training which is already far too long. The time taken to train a specialist should not exceed 6–7 years, and trained specialists deserve to be appointed to a permanent post by the age of 30–32 years. Research should be an optional extra for those with a real interest in such clinical or laboratory developments.

The paradox of prolonged training, long waiting lists for inpatient care, and an ever decreasing research output is fundamentally a result of the inadequate number of consultants allowed by our monopoly state employer. We have the least number of consultants per unit population compared with almost any other country in the Western world and have only 25% of consultants of other EEC countries (Innes Williams 1986). The 900 consultant obstetricians and gynaecologists in England and Wales is close to the number (850) of ACOG Members found in rural North Carolina and compares very unfavourably with the 3000 in New York State (Studd 1989). This demonstrates the shameful deficiencies in senior staffing levels in the NHS. These few are expected to cope with the vast clinical workload in obstetrics and gynaecology, the development and introduction of new techniques, teaching of trainees, audit, administration and the maintenance of a 'profile' at a local and international level as well as supervising the research that is becoming increasingly part of training.

Many more consultant posts are necessary in order to remove these anomalies but as little extra money will come from any government the principle way of achieving this will logically and inevitably be through funding from the private sector (Studd 1985). However, this realization is a long way off as few such posts, even those containing considerable research potential, are yet recognized for training or accreditation by the colleges.

Part of the solution to the manpower deficiency could be to make accredited (or even second year) senior registrars eight session consultants who would be allowed to make up their missing income from private practice or research sessions (Studd 1986). This would produce more real consultants at little extra cost, reduce the bottle neck, the length of training and the need for the irrelevant obstacles of an MD thesis or FRCS Diploma. It would also allow them time to develop new, yes even marketable, clinical skills. If any consultant doubts whether this scheme would be attractive to the trainees, I would challenge them to ask their registrar or senior registrar!

Two problems are indivisibly linked: the lack of consultant posts leads to the necessity to obtain the extra degree and academics, including myself, have a vested interest in having a continuous supply of able trainees to carry out research projects. Many trainees benefit from this period of research and it is clearly appropriate for the results to be published but I question whether the writing of an MD thesis is necessary for the vast majority.

Trainees are now too obsessed with the importance of obtaining a research job as they are aware that an MD will be seen as separating the successful from the failures at interview. They are also clearly aware that good clinical practice, labour ward and surgical skills and the kind care of patients have relatively little influence in promotion. If they are correct, and I believe they are, we have a great deal to put right. A change i our attitude to the importance of the MD and consideration o those professional qualities which discriminate between th good and the less good doctor, would be a start.

John Studd

Consultant Gynaecologis
King's College Hospital, Londo

References

Cameron M. (1984) Commentary. Obstetricians, gynaecologists an the FRCS (letter). *Br J Obstet Gynaecol* **91**, 407-408.

Innes Williams D. (1986) *Commission on the Provision of Specialis Services* Royal College of Surgeons, London.

Pinion S. (1991) Personal view. *Br Med J* **302**, 599.

Studd J. W. W. (1983) Commentary. Obstetricians, gynaecologists and the FRCS. *Br J Obstet Gynaecol* **90**, 785-786.

Studd J. W. W. (ed) (1989) Preface, *Progress in Obstetrics & Gynaecology,* Vol. **7**, p. v, Churchill Livingstone, London.

Studd J. W. W. (1985) Refuge in the private sector. *Br J Hosp Med* **33**, 7.

Studd J. W. W. (1986) Can private sector funds help the NHS? *Br J Hosp Med* **36**, 216-217.

British Journal of Obstetrics and Gynaecology
January 1992, Vol. 99, pp. 5–9

OBSTETRICS

Randomized trial of amniotomy in labour versus the intention to leave membranes intact until the second stage

JON F. R. BARRETT
Research Fellow
University of Newcastle
upon Tyne, UK

JOHN SAVAGE
Computor Liaison Officer
Leeds Polytechnic,
Calverley Street,
Leeds, UK

KEVIN PHILLIPS
SHO in Obstetrics and Gynaecology

RICHARD J. LILFORD
Professor and Head of Department of Obstetrics and Gynaecology
St James's University Hospital,
eckett Street, Leeds, UK

ABSTRACT

Objective To compare by randomized prospective clinical trial the outcome of labours which are managed with the intention to leave the membranes intact, compared with the practice of elective artificial rupture of the membranes (ARM) in early established labour.

Design Prospective randomized controlled trial of low risk women admitted in spontaneous labour, with intact membranes.

Setting The labour ward of St. James's University Hospital, Leeds, UK.

Subjects 362 women in spontaneous labour with intact membranes and no evidence of fetal distress, between 37 and 42 weeks gestation. During the course of the trial it was found that some randomization cards could not be accounted for and a system of daily checks was instituted. The results were analysed for all recorded women (n = 362) and after institution of the more rigorous system (n = 120).

Main outcomes measured The duration of each phase of labour, epidural rate, prevalence of an abnormal cardiotocograph (CTG) (assessed blind), method of delivery and neonatal outcome.

Results 178 of the 183 women (97%) in the ARM group had their membranes ruptured in early labour, and 83 (46%) of the 179 women allocated to non-intervention had ARM performed at some stage. A significant decrease in the duration of labour (mean 8·3, SD 4·1 h *vs* mean 9·7, SD 4·8h, n = 156; P = 0·05) was found amongst primigravidae allocated to ARM when compared with non intervention. The duration of the second stage of labour was unaffected. In the ARM group the epidural rate was higher and labour was more often complicated by CTG abnormalities. There were no differences in the method of delivery, fetal condition at birth (cord blood lactate, Apgar score) or postpartum pyrexia between the ARM and non-intervention groups. The same trends were observed when analysis was confined to women entered into the trial after the system of rigour was instituted.

Conclusion Routine ARM results in labour that is slightly shorter than if the membranes are allowed to rupture spontaneously but more epidurals are used suggesting that labour is more painful. There are fewer fetal heart rate abnormalities if the membranes are left intact but amniotomy has no effect on fetal condition at birth.

The decision whether, or when, to rupture the membranes in uncomplicated labour is a longstanding obstetric controversy. Artificial rupture of the membranes (ARM) is a widely advocated method of augmenting uncomplicated labour but a review of many studies has concluded that, 'there is an almost appalling contrast between the frequency with which augmentation of labour is employed in obstetric practice and the paucity of well controlled research data to judge the effectiveness of the interventions used for this purpose' (Keirse 1989). We describe a randomized study of routine ARM larger than those reported previously and with a greater number of measured outcomes.

Subjects and methods

A total of 398 women in established spontaneous labour at between 37 and 42 weeks gestation with intact membranes were entered into the trial. Women with any complication of pregnancy were excluded. Randomization was by numbered, sealed, opaque envelopes and was stratified by parity. Eligible women were entered on admission to the labour ward and the

---

Correspondence: J. F. R. Barrett, University of Newcastle upon Tyne, Princess Mary Maternity Hospital, Great North Road, Newcastle upon Tyne NE2 3BD, UK.

midwives were asked to record the subject's name and trial number in the register. The trial compared outcomes related to the *intention* to manage labour either by rupturing the membranes or allowing the membranes to rupture spontaneously. The labour ward staff could rupture the membranes at any time that they considered appropriate and they were encouraged to do so if they were unable to obtain a good external cardiotocograph (CTG) trace or if acceleration of labour was required. Once full dilatation was reached any membranes which had remained intact were ruptured. In all other respects labour management was identical. The outcomes assessed were (i) the duration of labour and the use of epidural analgesia and oxytocin, (ii) the method of delivery, (iii) CTG abnormality (decelerations) during labour and the presence of meconium-stained amniotic fluid at any time before delivery, (iv) fetal condition at birth (Apgar scores and cord blood lactate levels) and (v) the occurrence of postpartum pyrexia, defined as a temperature of >38°C at any time after delivery. It has been claimed that 'variable' decelerations are more common after ARM (Wetrich 1970; Keirse 1989). We determined the occurrence of early, late and variable decelerations as defined by Hon (1963) in the last hour of labour and in the preceding period. Each CTG trace was assessed by two of the authors, and scored without knowledge of the woman's group allocation or the outcome of labour. Differences of opinion were resolved by the senior author's 'blind' assessment.

It had been intended to measure the pain scores of subjects without epidural analgesia every hour on a linear scale, and to correlate the pain scores with cervical dilatation (Aitken 1969), but this objective was abandoned because our measurements were performed irregularly and we could not make the assessment blind. Also, epidural rates were very dissimilar in the two groups (see below) which would have confounded any comparison of mean pain scores. Immediately after delivery 2 ml of umbilical vein blood was aspirated from the cord and placed in a vial containing Long's medium and stored in a refrigerator at 4°C. The samples were analysed for lactic acid using an oxidase method within 24 h and discarded if this was not possible.

During the trial a discrepancy was discovered between the number of cards drawn and the number of women entered in the trial work-book; of the first 274 cards drawn, 32 were 'lost' because midwives had not recorded the names of women who were found not to be in labour and who were therefore discharged from the labour ward. For most of these women the randomization cards were lost by the time the woman was readmitted in established labour. However, we could not exclude the possibility that 'cheating' had occurred. We therefore instituted a system of rigour, whereby the trial register and envelopes were checked each morning to ensure that the trial work-book contained a record of each card drawn. After the institution of rigour all women for whom cards had been drawn but who were then found not to be in labour and discharged from the labour ward were identified. Their clinical notes were checked to ensure that the randomization card had been attached to the case record so that staff would be alerted to the woman's group allocation when she was later re-admitted in established labour. Only four of the subsequent 124 cards were unaccounted for. Thus, there was a total of 362 women in the trial, of which 120 were recruited after institution of rigour.

It was estimated ($\alpha = 0{\cdot}05$, $\beta = 0{\cdot}2$) that 158 women would be required in each group to show a doubling of the prevalence of fetal heartrate decelerations from 12% to 24%; 16 women in each group would be sufficient to demonstrate an increase in the duration of labour from 5 h to 6 h (assumed SD = 1 h) and an increase in cord blood lactate concentration from 1·0 to 1·2 μmol/l (assumed SD = 0·2); 91 women would be required in each group to show an increase in the epidural rate from 30% to 50%. Our trial was powerful enough to demonstrate effects of these sizes but 435 women in each group would have been needed to show a change in caesarean section rate from 5% to 10%.

Analysis of the entire trial group ($n = 362$) and a subgroup after institution of 'rigour' ($n = 120$) used the SPSS program. Students t-test was used for comparison of continuous variables, the χ^2-test was used for two by two tables and contingency tables for larger data sets and the Mann-Whitney U-test was used for comparing Apgar scores.

Results

1. *Entire trial group*

Compliance and comparability

We refer to the women allocated to have ARM as the ARM group and those for whom spontaneous rupture was intended are called the non-intervention group.

There were 362 recorded women in the trial of whom 183 were allocated to have ARM and 178 (97%) of them actually had ARM. ARM was also performed at some stage in 83 (46%) of the 179 women allocated to non-intervention. Of the 362 women in the trial 156 were nulliparous, 83 in the ARM group and 73 in the non-intervention group. Of the 73 nulliparae in the non-intervention group 36 (49%) completed the first stage of labour with intact membranes.

The mean cervical dilatation on entry to the study was 4·0 cm in the ARM group and 4·1 cm in the non-intervention group ($P = 0{\cdot}84$).

Duration of labour

The mean cervical dilatation at the time of rupture of membranes was 5·0 cm in the ARM group compared with 7·9 cm in the non-intervention group, although almost half the women in this group had ARM before spontaneous rupture or full dilatation.

A comparison of the duration of the stages of labour in the two groups is shown in Table 1. A slightly shorter first stage of labour was recorded in the ARM group but the difference was statistically significantly only in nulliparae. The duration of the second stage of labour was similar in the two groups. Oxytocin was used in 27 of the 183 (15%) women in the ARM group and in 16 of the 179 (9%) in the non-intervention group, the difference was not statistically significant ($P = 0{\cdot}12$, χ^2 with Yates' correction).

The women were all recruited shortly after admission to the labour ward and none of them had an epidural before entry into the trial. Epidural analgesia was used in 63 (34%) of the women in the ARM group compared with 39 (22%) in the non-intervention group ($P = 0{\cdot}01$) considering only the nulliparous women the corresponding numbers who had epidural anal-

Table 1. Comparison of the duration of labour in the two study groups

Duration of labour	ARM group	SRM group	Significance
First stage (h)*			
All women	7·4 (3·8) (n = 183)	7·7 (4·2) (n = 179)	NS
Nulliparae only	8·3 (4·1) (n = 83)	9·7 (4·8) (n = 73)	P = 0·05
Second stage (h)†			
All women	0·54 (0·24) (n = 178)	0·53 (0·25) (n = 177)	NS
Nulliparae only	0·82 (0·32) (n = 79)	0·84 (0·34) (n = 71)	NS

Results are mean (SD) values.
*According to the woman's history.
†According to diagnosis of second stage by midwife. Women delivered by caesarean section are excluded, all but one were nulliparae.
ARM = artificial rupture of membranes, SRM = spontaneous rupture of membranes.

gesia were 49 and 25 in the two groups, respectively (P = 0·15).

ethod of delivery

verall 90% of all the women in the study had spontaneous aginal deliveries, 8% were delivered by forceps and 2% by aesarean section. There were five caesarean sections and 16 orceps deliveries in the ARM group compared with two secons and 14 forceps deliveries in the non-intervention group. he difference in the methods of delivery between the two oups was not statistically significant, and there was also no tistically significant difference in the method of delivery tween the groups stratified by parity.

Analysis of the CTGs

CTGs were available for 344 women: 172 in each group (not all women were monitored). The prevalence of decelerations of all types before the last hour of labour was significantly higher in the ARM group (10%) compared with the non-intervention group (4%) (P = 0·04). There was no significant difference between the two groups in the prevalence of decelerations during the last hour of labour (19% *vs* 10%; P = 0·08). Table 2 shows that early and late decelerations occurred more often in the ARM group, although the numbers are small and the difference is not statistically significant.

Fetal condition

Meconium stained amniotic fluid was present in 15 of 183 (8%) of the women in the ARM group compared with 13 of the 179 (7%) in the non-intervention group (P = 0·8). Apgar scores were recorded in 356 infants, there was no significant difference in Apgar scores between the two groups (P = 0·8, Mann Whitney U-test). Umbilical vein lactate levels were measured after 192 deliveries, the mean cord lactic acid levels were 1·060 (SD 0·05) µmol/l in the ARM group and 1·057 (SD 0·07) µmol/l in the non-intervention group. Considering only the first born infants the corresponding values were 1·2 (SD 0·05) µmol/l in the ARM group and 1·20 (SD 0·06) µmol/l in the non-intervention group.

Postpartum pyrexia

The prevalence of postpartum pyrexia was similar in the two groups (11 of 183 in the ARM group and 9 of 179 in the non-intervention group).

2. *Results after introduction of 'rigour'*

The results in the last 120 women from whom data were recorded, after institution of rigour, were very similar to the results found in the entire trial group. Of the 50 women allocated to non-intervention 29 laboured with intact membranes until spontaneous rupture and this proportion (58%) was similar to that found in the group as a whole (54%). Mean cervical dilatation at entry to the study among all the women in the trial was 4·0 cm in the ARM group and 4·1 cm in the non-intervention group, the corresponding cervical dilatations (4·1 cm and 4·0 cm, respectively) in the two groups after the institution of rigour were almost identical.

The mean duration of labour was 6·8 (SD 3·1) h in the ARM group and 7·2 (SD 3·8) h in the non-intervention group. This difference was not statistically significant. These recorded durations were very similar to the corresponding durations of labour in the entire study group. After the institution of rigour there were no statistically significant differences between the ARM and non-intervention groups in the rate of spontaneous delivery, the use of oxytocin, the proportion of infants with low Apgar scores (<5) at 1 min and the epidural rate. Although the prevalence of fetal heart rate decelerations and epidural analgesia rate were statistically significantly different between the two groups in the study as a whole, they were not significantly different between the two groups after institution of rigour. They did, however, vary in the same direction and in similar proportions before and after rigour (Table 3).

Discussion

Arguments for and against ARM during spontaneous labour have been propounded by obstetricians over many years. The concept of a 'protective bag' around the baby buffering and protecting the infant from the immense forces of uterine contractions was suggested by Donald (1964), and was supported by Caldeyro-Barcia (1972) who suggested that ARM by increasing fetal head deformation or causing umbilical cord compression, led to a decrease in cord blood pH. Other reports (Martell *et al* 1976; Schwarcz *et al.* 1973; Steer 1976; Aldad-

Table 2. Prevalence of decelerations of different types before and during the last hour of labour in the two study groups

			Type of deceleration			
Stage of labour	Study group	n	None	Early	Late	Variable
Before last hour	ARM	172	154	9	7	2
	SRM	172	165	5	0	2
During last hour	ARM	172	140	14	9	9
	SRM	172	154	11	3	4

Abbreviations: ARM = artificial rupture of membranes, SRM = spontaneous rupture of membranes.

Table 3. Comparison of outcomes in the two study groups before and after institution of rigour

	Total group (n = 362)			After rigour (n = 120)		
Outcome	ARM (%)	SRM (%)	Significance	ARM (%)	SRM (%)	Significance
SVD	88·3	91·0	NS	87·7	90·5	NS
Decelerations on CTG*	10·5	4·1	$P<0{\cdot}05$	12·7	5·3	NS
Oxytocin usage	14·7	8·9	NS	15·5	11·5	NS
Epidural analgesia	34·4	21·8	$P = 0{\cdot}01$	36·0	23·0	NS

*Deceleration before the last hour of labour.

Abbreviations: ARM = artificial rupture of membranes, SRM = spontaneous rupture of membranes, SVD = spontaneous vaginal delivery.

jem 1977) have suggested that a transient decrease in uterine blood flow at amniotomy may lead to fetal distress. On the other hand, many obstetricians favour amniotomy because it is believed to accelerate labour and reveal the presence of any meconium-stained amniotic fluid.

The most clear cut differences between our study groups were the slightly decreased duration of labour and the higher epidural rate in the group allocated to ARM. Our findings confirm those of others (Stewart 1982; Gueressi *et al.* 1981; Wetrich 1970; Laros *et al.* 1972; Keirse 1989) that ARM accelerates labour but the use of oxytocin augmentation was not increased by non-intervention. A randomized study reported by Fraser *et al.* (1991) did not confirm acceleration of labour with ARM but that was a much smaller study in which shorter labours associated with ARM were not significantly different from the control group. There were virtually no differences in the rates of forceps delivery and caesarean section in our study. It should be noted however, that 'compliance' with 'non-intervention' was quite low, particularly among nulliparous women of whom half eventually had their membranes ruptured artificially, albeit at a much later stage of labour. We are not certain why the attending midwives performed an amniotomy in such a high proportion of women allocated to non-intervention. Amniotomy was left to their discretion but was encouraged by the trial protocol if slow progress was evident or if an unsatisfactory external CTG was recorded. It is noteworthy that where the membranes were ruptured in the non-intervention group this took place at a greater mean cervical dilatation than in the ARM group.

ARM allows the identification of meconium staining of the amniotic fluid, widely accepted as an indicator of possible fetal distress. However, with the advent of cardiotocography, the presence of meconium without concomitant CTG abnormality is unlikely to change the management plan in a normally progressing labour. The notion that internal monitoring provides a better assessment of baseline variability may have been overstated and the use of a fetal scalp electrode is not without risks (Siddiqi 1982; Fernandez 1983; Guill 1982; Nieburg 1987). If a completely normal tracing is obtained using external cardiotocography, there is probably little to be gained from more invasive internal monitoring (Keirse 1981).

We have confirmed the observations of others (Sims & Thiery 1980) that ARM increases the occurrence of fetal heart rate decelerations. The epidural rate was also higher if the membranes were ruptured, which could be a confounding factor. On the other hand, it may be relevant that Miyazaki & Taylor (1983) showed marked improvement in 'variable' decelerations if the volume of amniotic fluid was artificially increased by infusing normal saline into the amniotic cavity.

Unlike Caldeyro-Barcia (1972), we found no increase in acidosis following planned ARM. This may be because we measured lactic acid rather than pH. Acute CO_2 retention during delivery may cause respiratory acidosis but that is not important if there is no concomitant metabolic acidosis. Other studies have also disputed the finding of acidosis in association with amniotomy (Martell *et al* 1976; Laros *et al.* 1972).

We think our experience with lost trial envelopes will be valuable to other obstetricians planning labour ward trials and we believe that if numbered cards are used for randomization, then authors should state the number of cards drawn and the number of patients entered. Fifty midwives work in our labour ward and vigilance is needed in the conduct of trials of intrapartum care. We are now using the labour ward computer t automate further clinical experiments. This reduces the work load (and therefore the cost) of trials and eliminates the possibility of losing patients after randomization (Johnson & Lilford 1990). In this particular instance loss of patients in the early phase of the trial did not seem to bias our results becaus the effects of the treatment policies were the same in th second, rigorous phase of the study. For some observations th differences in outcome were not statistically significant but th direction and size of change was the same suggesting tha statistical significance may have been masked by type 2 error.

We conclude that early artificial membrane rupture does not compromise neonatal outcome, however, this policy leads to an increase in fetal heart rate decelerations and in the use of epidural analgesia. We did not show a statistically significant increase in the use of operative delivery which might have been expected as a result of the higher prevalence of fetal heart rate abnormalities, perhaps because even this study was too small to show a small but important increase in this end point.

Acknowledgments

We would like to thank the labour ward midwives who managed the patients in this study as well as Mr K. Aulton, Chief MLSO, Department of Pathology, St James's Hospital Leeds, for carrying out the lactic acid assays.

References

Aitken R. C. B. (1969) Measurement of feelings using visual analogue scores. *Proc Roy Soc Med* **92**, 989-993.

Aldadjem S. & Miller T. (1977) Effects of spontaneous and artificial membrane rupture in labour on fetal heart rate patterns. *Br J Obstet Gynaecol* **84**, 44-47.

Caldeyro-Barcia R. (1972) Effects of rupture of membranes on fetal heart rate patterns. *Int J of Gynaecol Obstet* **10**, 169-172.

Donald I. (ed.) (1964) *Practical Obstetric Problems*, Third edition, Lloyd-Luke Ltd., London, p. 420.

Fernandez C. M. (1983) Complications of fetal scalp electrodes. *Am J Obstet Gynecol* **145**, 891.

Fraser W. D., Sauve R., John Parboosingh I., Fung T., Sokol R. & Persaud D. (1991) A randomized controlled trial of early amniotomy. *Br J Obstet Gynaecol* **98**, 84-91.

Gueressi E., Gori G., Beccari A., Farro M. & Mazzonti C. (1981) Influence of spasmolytic treatment and amniotomy on delivery times: A factorial clinical trial. *Clin Ther* **3**, 382-388.

Guill M. A. (1982) Neonatal herpes simplex associated with fetal scalp electrodes. *J Am Acad Dermatol* **7**, 408-409.

Hon E. H. (1963) The classification of fetal heart rate. *Obstet Gynecol* **22**, 137-146.

Johnson N. & Lilford R. J. (1990) Computerized automation of clinical trials in computing and decision support in obstetrics and gynaecology. *Bailleres Clin Obstet Gynaecol*, **4**, 781-786.

Keirse M. J. N. C., Trimbos J. B., Mallens T. E. J. M. & Van der Heemst M. (1981) Reliability of ultrasound as compared to direct fetal electrocardiography for ante-partum cardiotococardiography. *Br J Obstet Gynaecol* **88**, 391-394.

Keirse M. J. N. C. (1989) Augumentation of labour. In *Effective Care in Pregnancy and Childbirth* (Chalmers I., Enkin M. & Keirse M. J. N. C., eds), Oxford University Press, Oxford, p. 964.

Laros R. K., Work B. A. & Witting W. C. (1972) Amniotomy during the active phase of labour. *Obstet Gynecol* **39**, 702-704.

Martell M., Belizan J. M., Nieta F. & Schwarcz R. (1976) Blood acid-base balance at birth in neonates from labours with early and late rupture of membranes. *J Pediat* **89**, 963-967.

Miyazaki F. S. & Taylor N. A. (1983) Saline amnioinfusion for relief of variable or prolonged decelerations. *Am J Obstet Gynecol* **146**, 670-678.

Nieburg P. (1987) CSF leak associated with fetal scalp electrodes. *Am J Obstet Gynecol* **7**, 839-840.

Schwarcz R., Althabe O., Belitzky R., *et al.* (1973) Fetal heart rate patterns in labors with intact and with ruptured membranes. *J Perinat Med* **1**, 153-165.

Siddiqi L. (1982) Nectrotizing fasciitis of the scalp. *Am J Dis Child* **136**, 226-228.

Smis L. & Thiery M. (1980) Fetal heart rate patterns before, during and after amniotomy. *Euro J Obstet Gynaecol Reprod Biol* **11**, 163-171.

Steer P. (1976) Effect of membrane rupture on fetal heart rate patterns in induced labour. *Br J Obstet Gynaecol* **83**, 454-459.

Stewart P. (1982) Spontaneous labour: when should the membranes be ruptured. *Br J Obstet Gynaecol* **89**, 39-43.

Wetrich D. W. (1970) Effect of amniotomy upon labour, a controlled study. *Obstet Gynecol* **35**, 800-808.

Received 11 September 1990
Resubmitted 20 May 1991
Accepted 16 July 1991

British Journal of Obstetrics and Gynaecology
January 1992, Vol. 99, pp. 10–12

OBSTETRICS

Changes in decidual stromal cell function associated with labour

HAROON KHAN
Research Fellow
OSAMU ISHIHARA
Visiting Research Fellow
MARK H. F. SULLIVAN
Lecturer in Biochemistry
MURDOCH G. ELDER
Professor of Obstetrics & Gynaecology

Institute of Obstetrics and Gynaecology, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0HS, UK

ABSTRACT

Objective To determine whether decidual cells produce altered levels of prostaglandins after labour.

Design Decidual stromal cells and macrophages were isolated before and after labour, and the production of prostaglandins E_2 and $F_{2\alpha}$ measured. Changes in the numbers of cyclooxygenase enzyme positive cells were assessed by immunocytochemistry.

Results Decidual stromal cells obtained after labour produced 30 times more prostaglandins E_2 and $F_{2\alpha}$ in culture than cells obtained before labour. The increased production persisted for up to 72 h of culture, and was associated with an increase in the numbers of cyclooxygenase-positive cells from <5% to >95%. No changes in macrophage function were observed.

Conclusion Increased levels of prostaglandins E_2 and $F_{2\alpha}$ were released from decidual stromal cells after labour, suggesting that these cells may be an important source of prostaglandins in labour.

The importance of the prostaglandins E_2 and $F_{2\alpha}$ (PGE_2 and $PGF_2\alpha$, respectively) in human labour has been well established (MacDonald *et al.* 1978; Turnbull 1983), but the tissues which are the major source of these prostaglandins in labour have not been identified so securely. A number of studies have investigated the control of PGE_2 production by the amnion (Bleasdale & Johnston 1984; Mitchell 1986; Casey *et al.* 1988; Lopez Bernal *et al.* 1989; Romero *et al.* 1989), and also determined changes in PGE_2 production by this tissue associated with labour (Okazaki *et al.* 1981; Skinner & Challis 1985; McCoshen *et al.* 1987), but recent results suggest that very little of the PGE_2 synthesized in the amnion is likely to cross the choriodecidua without being metabolized (McCoshen *et al.* 1990; Roseblade *et al.* 1990), and is thus unlikely to be of importance in the initiation of labour. Other workers have implicated the decidua in preterm labour associated with maternal intrauterine infection (Casey *et al.* 1989; Romero *et al.* 1988), but the relation between this pathological labour and normal term labour is not known.

To examine the possible role of decidual cells in labour, we investigated the production of PGE_2 and $PGF_{2\alpha}$ by this tissue before and after labour. Preliminary results were very variable, which was thought to be due to the heterogeneity of this tissue; it is known that term human decidua contains both stromal cells and macrophages (Bulmer *et al.* 1988), so we determined the effects of labour on both cell types.

Materials and methods

Human decidual cells were obtained from fetal membranes at the time of delivery by elective caesarean section in four women, or after spontaneous vaginal delivery in four women. None of the women had been treated with anti-inflammatory drugs such as aspirin or indomethacin, and none had any pathological condition.

Decidual tissue was scraped off the fetal membranes with a razor and treated with two step digestion with dispase (grade II, BCL) (10 mg/ml), followed by hyaluronidase (Type Is, Sigma) (2 mg/ml), collagenase (Type IV, Sigma) (300 U/ml) and deoxyribonuclease (Type IV, Sigma)(50 µg/ml)(Vince *et al.* 1990; Khan *et al.* 1991). Purification of stromal cells was achieved with a Percoll (Pharmacia) discontinuous density gradient method which was slightly modified from that described by Matsui *et al.* (1988). Briefly, we layered 60%, 40%, 20% and 5% Percoll solution in order and centrifuged at 2700 *g* for 20 min with 10–20 × 10^6 cells in each tube. Stromal cells were recovered in the 20% Percoll fraction (SG 1·033). Decidual stromal cells or macrophages were cultured at a concentration of 1 × 10^6 cells/2 ml of 199 medium (GIBCO) containing 10% horse serum (GIBCO) and 1% L-glutamine (GIBCO). The cells were cultured overnight at 37°C in 95% air: 5% CO_2) for 24 h to allow recovery from the preparative procedures used.

Quadruplicate samples of decidual stromal cells and macrophages from each pregnancy were incubated for 24 h on each day of culture, after which the media were collected from the wells and cell viability was determined by trypan blue exclusion test. The samples were frozen at –20°C until radioimmunoassay for PGE_2 and $PGF_{2\alpha}$.

Decidual stromal cells to be used in immunocytochemical studies were cultured on glass cover-slips, and cyclooxygenase enzyme was assessed by immunocytochemistry using a mono-

Correspondence: H. Khan.

Table 1. Production of prostaglandins E_2 and $F_{2\alpha}$ by decidual stromal cells*

Prostaglandin	Cells obtained after Vaginal delivery (labour)	 Abdominal delivery (no labour)	95% CI of difference between means
PGE_2 (ng/10^6 cells/24 h)			
0-24 h	28·6 (2·7)	0·2 (0·1)	24·3 to 32·5
24-48 h	18·4 (1·1)	1·6 (1·2)	13·3 to 20·3
$PGF_{2\alpha}$ (ng/10^6 cells/24 h)			
0-24 h	34·2 (6·2)	1·0 (0·3)	23·3 to 43·1
24-48 h	32·8 (4·3)	1·8 (0·2)	24·0 to 38·0

*Fetal membranes were obtained before or after the onset of labour and PGE_2 or $PGF_{2\alpha}$ production determined. All data are means (SD) (from four pregnancies). 95% CI represents the 95% confidence interval for the difference between prostaglandin production after labour and before labour.

clonal antibody to cyclooxygenase enzyme obtained from Cayman Chemical Co and a Vectastain kit (Vector Labs), as described in detail elsewhere (Khan *et al.* 1991). A total of 500 cells was counted in each experiment to assess the extent of cyclooxygenase staining. Data from cells obtained from all four caesarean sections were combined and compared with combined data from cells from vaginal deliveries and analysed using Student's *t*-test.

Results

PGE_2 production by decidual stromal cells obtained before the onset of labour was in the range 0·1–1·0 ng/10^6 cells/24 h, which is similar to values reported in previous work on decidual cells (Okazaki *et al.* 1981). Substantially increased ($P<0·001$) levels of PGE_2 were produced by decidual stromal cells obtained after the onset of labour (Table 1). This increase in PGE_2 production persisted for at least 48 h of culture in the absence of added stimuli, which suggested that some form of decidual activation had occurred that involved a major change in decidual stromal cell function. The production of $PGF_{2\alpha}$ was also elevated after labour, and this increase was maintained up to 72 h of culture (Table 1).

Studies in this department have suggested that prostaglandin production by decidual stromal cells is dependent on extracellular arachidonic acid (Ishihara *et al.* unpublished obser-

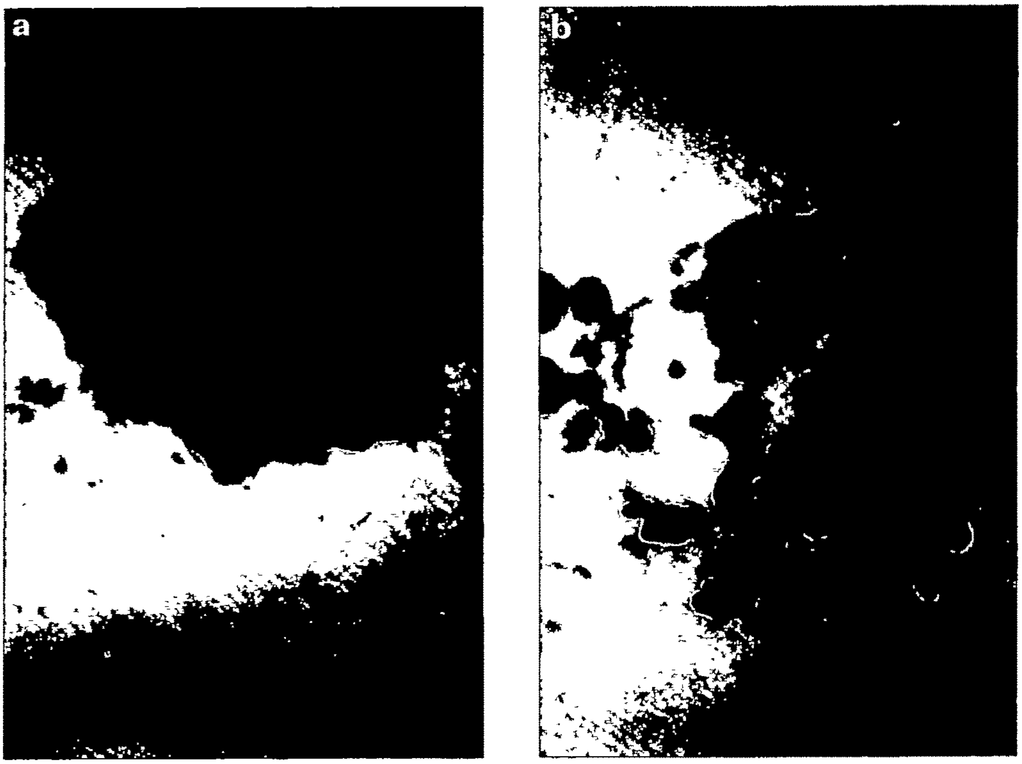


Fig. 1. Immunocytochemical staining for cyclo-oxygenase enzyme in decidual stromal cells obtained after (a) or before (b) labour.

vations), and that changes in the levels of the cyclooxygenase enzyme may therefore be important in the regulation of prostaglandin production by these cells. Accordingly, immunocytochemistry was used to assess changes in cyclooxygenase enzyme levels in decidual stromal cells obtained before and after labour. It was readily apparent that the staining for cyclooxygenase enzyme was far higher in cells obtained after labour compared with the same cell population obtained before labour (Figure 1a and b). The mean proportion of decidual stromal cells obtained before labour that stained positively for cyclooxygenase was 3% (SD 2) compared with 95% (SD 3) of the cells obtained after labour. Similar results (not shown) were obtained in two further experiments.

PGE_2 production by decidual macrophages was unaffected by labour (before labour mean 3·4, SD 0·9 ng/10^6 cells/24 h, $n = 3$; after labour 3·1, SD 0·3 ng/10^6 cells/24 h, $n = 3$).

Discussion

In this study we have investigated the production of PGE_2 and $PGF_{2\alpha}$ by the two main cellular components of human decidua, and found that decidual stromal cells produce >30 times as much of both prostaglandins after labour as beforehand. This is markedly greater than the increases shown for other components of fetal membranes, which have been reported to be 2–5 fold (Okazaki *et al.* 1981; Skinner & Challis 1985; McCoshen *et al.* 1987, 1990), which suggests that the decidual stromal cells are a major source of prostaglandins in human labour. This finding is consistent with the studies implicating the decidua in preterm labour associated with intrauterine infection (Romero *et al.* 1988; Casey *et al.* 1989), and implies that increased decidual prostaglandin production may be important in normal term labour. It is also apparent that the decidual macrophages, which account for 20% of the term decidua (Bulmer *et al.* 1988; Vince *et al.* 1990), are unlikely to be a major source of PGE_2 in term labour, although it is still possible that the macrophages may be involved in some of the inflammatory mechanisms associated with labour (Romero *et al.* 1988).

Little is known of the control of decidual stromal cell prostaglandin production, since most studies with this tissue have used mixed cell populations containing both stromal cells and macrophages (Okazaki *et al.* 1981; McCoshen *et al.* 1987). Our results indicate that increased synthesis of the cyclooxygenase enzyme may be involved in the increase in prostaglandin production by decidual stromal cells after labour, but further studies are required to elucidate the intracellular mechanisms involved.

References

Bleasdale J. E. & Johnson J. M. (1984) Prostaglandins and human parturition: regulation of arachidonic acid mobilization. *Rev Perinat Med* 5, 151-191.

Bulmer J. N., Pace D. & Ritson A. (1988) Immunoregulatory cells in human decidua: morphology, immunochemistry and function. *Reprod Nutr Develop* **28**, 1599-1614.

Casey M. L., Korte K. & MacDonald P. C. (1988) Epidermal growth factor stimulation of prostaglandin E_2 biosynthesis in amnion cells. *J Biol Chem* **263**, 7846-7854.

Casey M. L., Cox S. M., Beutler B., Milewich L. & MacDonald P. C. (1989) Cachetin/tumour necrosis factor-α formation in human decidua. *J Clin Invest* **83**, 430-436.

Khan H., Ishihara O., Sullivan M. H. F. & Elder M. G. (1991) A comparison of two decidual cell populations by immunocytochemistry and prostaglandin production. *Histochemistry* (in the press).

Lopez Bernal A., Newman G. E., Phizackerley P. J. R. & Turnbull A. C. (1988) Surfactant stimulates prostaglandin E production in human amnion. *Brit J Obstet Gynaecol* **95**, 1013-1017.

MacDonald P. C., Porter J. C., Schwartz B. E. & Johnston J. M. (1978) Initiation of parturition in the human female. *Semin Perinatal* **2**, 273-297.

McCoshen J. A., Johnson K. A., Dubin N. H. & Ghodgaonkar R. B. (1987) Prostaglandin E_2 release on the fetal and maternal sides of the amnion and chorion-decidua before and after term labour. *Am J Obstet Gynecol* **156**, 173-178.

McCoshen J. A., Hoffman D. R., Kredentser J. V., Arenada C. & Johnston J. M. (1990) The role of fetal membranes in regulating production, transport, and metabolism of prostaglandin E_2 during labour. *Am J Obstet Gynecol* **163**, 1632-1640.

Matsui S., Yoshimura N. & Oka T. (1988) Characterization and analysis of soluble suppressor factor from early human decidual cells. *Transplantation* **47**, 678-680.

Mitchell M. D. (1986) Regulation of eicosanoid biosynthesis during pregnancy and parturition. In *Advances in Eicosanoid Research* (Hillier, K., ed.), MTP Press, Lancaster, UK. pp. 108-127.

Okazaki T., Casey M. L., Okita J. R., MacDonald P. C. & Johnston J. M. (1981) Initiation of human parturition. XII. Biosynthesis and metabolism of prostaglandins in human fetal membranes and uterine decidua . *Am J Obstet Gynecol* **139**, 373-381.

Romero R., Durum S., Dinarello C. A., Oyarzun E., Hobbins J. C. & Mitchell M. D. (1989) Interleukin-1 stimulates prostaglandins biosynthesis by human amnion. *Prostaglandins* **37**, 13-22.

Romero R., Mazor M., Wu Y. K., Sirtori M., Oyarzun E., Mitchell M. D. & Hobbins J. C. (1988) Infection in the pathogenesis of preterm labour. *Semin Perinatol* **12**, 262-279.

Roseblade C. K., Sullivan M. H. F., Khan H., Lumb M. R. & Elder M. G. (1990) Limited transfer of prostaglandin E_2 across the fetal membranes before and after labour. *Acta Obstet Gynecol Scand* **69**, 399-403.

Skinner K. A. & Challis J. R. G. (1985) Changes in the synthesis and metabolism of prostaglandins by human fetal membranes and decidua at labor. *Am J Obstet Gynecol* **151**, 519-523.

Turnbull A. C. (1983) Human parturition: historic development and overview. In *Initiation of Parturition: Prevention of Prematurity.* (MacDonald P. C. & Porter J., eds), Ross Laboratories, Columbus, Ohio. pp. 87-104.

Vince G. S., Starkey P. M., Jackson M. C., Sargent I. L. & Redman C. W. G. (1990) Flow cytometric characterization of cell populations in human pregnancy decidua and isolation of decidual macrophages. *J Immunol Methods* **132**, 181-189.

Received 12 March 1991
Accepted 18 August 1991

British Journal of Obstetrics and Gynaecology
January 1992, Vol. 99, pp. 13–17

OBSTETRICS

Does admission to hospital for bed rest prevent disease progression or improve fetal outcome in pregnancy complicated by non-proteinuric hypertension?

C. A. CROWTHER
Lecturer

A. M. BOUWMEESTER
Registrar

Department of Obstetrics &
Gynaecology,
Harare Central Hospital, PO Box
ST14, Southerton, Harare, Zimbabwe

H. M. ASHURST
Computing Co-ordinator

National Perinatal Epidemiology Unit,
Radcliffe Infirmary, Oxford OX2 6HE,
UK

ABSTRACT

Objective To test whether a policy of admission to hospital for rest is of value in the management of women with non-proteinuric hypertension during pregnancy.
Design A randomized controlled trial.
Setting Harare Maternity Hospital, Zimbabwe.
Subjects 218 (28 first pregnancies) women with non-proteinuric hypertension and a singleton pregnancy at between 28 and 38 weeks gestation allocated to rest in hospital or routine outpatient care.
Intervention Admission to hospital for rest. Encouraged to rest in bed although voluntary ambulation around the ward was allowed. The women in the control group were encouraged to continue normal activity at home, to check urine each day for proteinuria. All the women were reviewed weekly.
Main outcome measures Disease progression was assessed by the development of severe hypertension (≥160/110 mmHg), development of proteinuria, need for induction of labour and number of infants born preterm (<37 weeks). Fetal outcome was assessed by birthweight, number of infants small-for-gestational age (SGA), and the number of infants requiring admission to the neonatal unit and their length of stay.
Results The hospital rest group had a decreased risk of developing severe hypertension (blood pressure ≥160/110 mmHg [odds ratio 0·47, 95% CI 0·26–0·83]). No differences were found in fetal growth or neonatal morbidity. The mean antenatal stay in hospital was 22·2 (SD 16·5), and 6·5 (SD 7·9) days in the rest and control groups, respectively.
Conclusions Hospital admission for bed rest decreased the risk of developing severe hypertension but no improvement in fetal growth or neonatal morbidity was observed. Fetal monitoring at home and continued outpatient antenatal care provided a safe, alternative policy to hospital admission.

Pregnancy complicated by hypertension is associated with high maternal and perinatal mortality and morbidity (Butler & Alberman 1969; Chamberlain *et al.* 1978; DHSS 1986). Hypertensive diseases of pregnancy remain one of the commonest causes of maternal death in England and Wales (DHSS 1986) and in Harare, Zimbabwe (Crowther 1986a). Management of hypertension during pregnancy, based largely on clinical experience rather than the results of randomized controlled trials, rests on screening, early diagnosis, admission to hospital to enable vigilant observation and timely delivery, ideally before symptoms develop. Admission to hospital is accepted practice worldwide and achieves the two objectives of bed rest and close maternal and fetal monitoring (Gant & Worley 1980; Davey & Dommisse 1980; MacGillivray 1983a).

Admission to hospital for bed rest in pregnancy complicated by hypertension was first introduced in Australasia in the 1950s as part of a management package to reduce the incidence of pre-eclampsia and to abolish eclampsia (Hamlin 1952; Dawson 1953; Hughes 1956). It became common practice to admit women developing hypertension in pregnancy to hospital for rest.

Hospital admission for bed rest could, in theory, prevent or delay progression of the hypertension and so improve pregnancy outcome. These benefits need to be demonstrated since admission for bed rest is expensive (Powers & Miller 1979), often socially disruptive and stressful (Kramer *et al.* 1986) and potentially hazardous because of thromboembolic events (DHSS 1986).

In spite of its widespread use, we are aware of only one published randomized trial assessing the value of admission to hospital for bed rest in asymptomatic, non-proteinuric hypertension (Mathews 1977). Mathews concluded that 'so long as adequate supervision can be given without them, then bed rest

Correspondence: Dr C. A. Crowther, Department of Obstetrics & Gynaecology, University of Adelaide, GPO Box 498, Adelaide, South Australia 5001.

in hospital and mild sedation (with phenobarbitone) are of no value to the majority of patients with non-albuminic and non-symptomatic hypertension in advanced pregnancy.' He also concluded that self-monitoring at home for the premonitory signs of eclampsia and proteinuria did not appear to increase the risks to the mother or the fetus and urged that these findings be checked by others.

Given the challenge from Mathews (1977) and the common use of admission to hospital for bed rest in pregnancies complicated by non-proteinuric hypertension at Harare Maternity Hospital (Crowther 1986a) and in addition the increasing pressure on the antenatal wards, we decided to organize a randomized controlled trial to assess the current policy of admitting all pregnant women for bed rest with a blood pressure of ≥140/90 mmHg compared with continued outpatient management.

Subjects and methods

The study objectives were to compare admission to hospital for bed rest with outpatient care in non-proteinuric hypertension with respect to prevention or delay in progression of the hypertension, fetal growth and neonatal outcome. The principal measures of outcome were development of severe hypertension (≥160/110 mmHg), proteinuria (≥1+ Albustix testing), birthweight and need for admission and length of stay on the neonatal unit.

The principal outcome to detect progression of the disease was the frequency of proteinuria which, from previous observations in the trial population, was estimated to be 30% at delivery (Crowther 1986b). A trial size of 220 women had an 80% chance (β-error 0·20) of detecting a statistically significant difference at the 5% level (α-error 0·05) if the frequency of developing proteinuria was reduced by half by admission to hospital for bed rest. The researcher making the gestational age assessments (Dubowitz *et al.* 1970) was unaware of the woman's allocated management. Masking was not possible for the blood pressure measurements and proteinuria assessments, but the other primary measures of outcome (birthweight, need for admission to the neonatal unit) were measurements or decisions taken by staff who were unaware to which management the mother had been allocated.

Severe hypertension was defined as blood pressure ≥160/110 mmHg, severe proteinuria as ≥3+ on Albustix testing, preterm as <37 completed weeks gestation, low birthweight as <2500 g and small-for-gestational age as birthweight <10th centile by local singleton standards.

Statistical analysis was by the Student's *t*-test to compare means, and odds ratios to compare frequencies between groups; 95% CI of the odds ratio were derived as recommended by Katz *et al.* (1978). There were no interim analyses. The University Research Board gave approval for the study.

The Greater Harare obstetric unit supervises over 40 000 deliveries each year, over half (low risk) in 13 clinics in the residential suburbs and the remainder (high risk) in the central referral unit at Harare Maternity Hospital. A special hypertension antenatal clinic was established at the hospital during 1984. Women with a singleton pregnancy attending this clinic or admitted to the antenatal ward with a blood pressure of ≥140/90 mmHg but no proteinuria (or only a trace on Albustix testing) at between 28 and 38 weeks gestation were considered for entry into the trial which ran from 1985 to 1986. Women were excluded if they were symptomatic, had a diastolic blood pressure ≥110 mmHg, a caesarean section scar or an antepartum haemorrhage during the pregnancy.

Block randomization was used, stratified into three groups: (i) primigravidae, (ii) multigravidae known to have chronic hypertension (defined as the presence of persistent hypertension ≥140/90 mmHg from whatever cause before pregnancy or ≤20 weeks gestation) and (iii) multigravidae not known to have chronic hypertension. The researchers involved in treatment allocation were not involved in making the randomization schedule. Women who gave verbal consent were recruited and allocated to a study group by opening the next in a series of consecutively numbered, opaque, sealed envelopes in the correct stratification group. The woman was allocated according to the enclosed instructions to the hospital rest group or control group.

Women allocated to the hospital rest group were requested to attend the antenatal ward at their nearest maternity clinic as soon after recruitment as was convenient. All were encouraged to rest in bed as much as possible. although voluntary ambulation around the ward was allowed. The clinic staff kept a 4 h record of blood pressure and tested the urine daily for proteinuria.

Women allocated to the control group were encouraged to continue their normal activities at home and no particular restrictions were advised. If they were recruited on the antenatal ward, they were sent home. They were instructed on how to test their urine for proteinuria and supplied with a container of Albustix and asked to check their urine each day for proteinuria. Each woman took home a printed instruction sheet.

All the women were asked to record the number of fetal movements over a 2 h period each morning. They were reviewed weekly. Those in hospital were seen on the wards and the control women were seen in the antenatal clinic. Weekly assessments made included maternal weight, blood pressure and urinalysis, full blood count and renal function tests.

The clinic staff (hospital rest group) and the women themselves (control group) were instructed that the women should go to Harare Maternity Hospital immediately if labour started or if any of the following abnormalities occurred; proteinuria (≥1+ on Albustix testing), fetal movements were reduced or ceased, symptoms developed suggestive of fulminating pre-eclampsia such as headache, problem with their eyesight, abdominal pain, or any other problem which concerned them. Clinic staff transferred the women in the hospital rest group to Harare Maternity Hospital and the control women were admitted from the antenatal clinic to the hospital, if their blood pressure rose to ≥160/110 mmHg. Labour was induced if complications developed requiring delivery or, at 40 weeks gestation, if spontaneous labour had not started.

Results

Overall 110 women were randomized to be managed by rest in hospital and 108 were randomized to the control group. The characteristics of the women were comparable between the two groups (Table 1). Results were analysed according to allocation at randomization despite non-compliance, which was rare. Thus, 3 (3%) of the 110 women allocated to the hospital

Table 1. Characteristics of the two study groups

	Hospital rest (n = 110)	Control (n = 108)
Age (years)	28·9 (6·6)	28·7 (6·3)
Primigravidae	14	14
Multigravidae		
without chronic hypertension	81	76
with chronic hypertension	15	18
Height (cm)	158 (8·2)	160 (7·9)
Weight at entry (kg)	75·8 (12·5)	78·2 (13·3)
Gestation at entry (weeks)		
Primigravidae	35·0 (2·3)	35·4 (2·8)
Multigravidae		
without chronic hypertension	35·5 (2·6)	34·7 (3·2)
with chronic hypertension	34·3 (2·9)	33·7 (3·0)
Total	35·3 (2·6)	34·6 (3·0)
Blood pressure at entry (mmHg)		
Systolic	150·7 (10·8)	150·9 (11·6)
Diastolic	97·8 (5·3)	97·4 (5·0)
Mean arterial	115·4 (6·1)	115·3 (6·0)
Proteinuria trace	28 (26)	16 (15)

Results are means (SD) or n (%) values as appropriate.

rest group did not attend for bed rest and only presented to the hospital in labour. These women are included in the hospital rest group, as are a further 5 (5%) women who required a short leave of absence from hospital for domestic reasons (mean 5·6 days, SD 2·4). Transfer from the resting clinic to hospital was necessary for 53 (48%) women in the hospital rest group for reasons other than labour. Similarly, 62 (57%) of the 108 women in the control group subsequently required antenatal admission to the hospital because their condition worsened (blood pressure ≥160/110 mmHg or proteinuria ≥1+) but their data are analysed with the control group. Their mean gestation at admission was 37·1 weeks (SD 2·4), on average 1·8 weeks later than the admission gestation for the hospital rest group. The mean length of antenatal stay in the hospital rest group was 22·2 days (SD 16·5) and in the control group 6·5 days (SD 7·9).

Pregnancy outcome

Details of pregnancy outcome are given in Table 2. Fewer women in the hospital rest group developed severe hypertension (odds ratio 0·47, 95% CI 0·26–0·83). Proteinuria developed in a similar proportion of women in each group although fewer women (24, 22%) in the hospitalized group developed severe (≥3+) proteinuria compared with the control group (34, 32%). The data show that rest in hospital had no effect on the mean length of gestation, the proportion of women requiring induction of labour or on the mode of delivery. There were, however, fewer preterm deliveries in the hospital rest group (odds ratio 0·48, 95% CI 0·24–0·97), an effect mainly due to the subgroup of multigravidae without chronic hypertension.

Fetal outcome

Overall there were no differences in the mean birthweight, number of low-birthweight infants or small-for-gestational age infants between the two management groups. However, as was predictable from the lower proportion of preterm deliveries in the subgroup of multigravidae without chronic hypertension in the hospital rest group, there was a lower proportion of low-birthweight infants in this subgroup (odds ratio 0·34, 95% CI 0·13–0·91). No differences were observed in neonatal morbidity as reflected by the need for admission to the neonatal unit or length of stay.

There were two perinatal deaths in the hospital rest group, both were normally formed stillbirths. One of these women had failed to attend for hospital admission for rest when recruited at 34 weeks, with a blood pressure of 150/110 mmHg. She presented in labour at 37 weeks when the fetal heart was not detectable. The other woman was admitted for rest at the clinic at 37 weeks with a blood pressure of 140/90 mmHg. She was transferred to Harare Maternity Hospital in labour at 40 weeks but the fetal heart had stopped on arrival. One baby in the control group died in the early neonatal period from intrapartum asphyxia. The primigravid mother was recruited at 37 weeks with a blood pressure of 140/90 mmHg and no proteinuria. She began labour spontaneously at 40 weeks and was delivered by vacuum extraction because of late decelerations and a delayed second stage.

Discussion

This study provides evidence from a controlled trial that hospital bed rest in pregnancy complicated by non-proteinuric hypertension prevents the progression of the disease by decreasing the risk of developing severe hypertension. This beneficial effect was only seen in parous women, but was not associated with any overall improvement in fetal growth and reduced neonatal morbidity. It is notable that self-monitoring at home for proteinuria and reporting to the hospital if proteinuria developed, fetal movements decreased or symptoms of pre-eclampsia developed, did not appear to increase the risks to the mother or her baby compared with hospitalization for bed rest, so confirming the findings of Mathews (1977). No problems were encountered in teaching the women allocated to home management to self-test their urine daily. Based on a colour change, even those women who could not read were able to perform the urinalysis satisfactorily and recognize a clinically significant result. The control group had a mean length of antenatal hospital stay 15·7 days less than the hospital rest group. Factors such as the financial saving on inpatient care, easing of pressure on the antenatal wards and permitting the woman to continue her normal activities at home need to be considered when determining management policies.

The policy of admission to hospital for bed rest decreased the risk of developing severe hypertension. The severity of hypertension developed correlates with the risk to the mother and the fetus (Friedman & Neff 1976; MacGillivray 1983b) and most authorities would treat blood pressures of ≥160/110 mmHg with antihypertensives (Gant & Worley 1980) to reduce the risks of hypertensive cerebral haemorrhage and hypertensive encephalopathy. Therapy that can significantly reduce the risk of progression to severe hypertension requiring anti-hypertensive treatment would be expected to improve fetal growth and decrease fetal morbidity. Such benefit in fetal growth was only evident as a reduced risk of low birthweight in the multigravidae without chronic hypertension in the hospital

Table 2. Pregnancy outcome in the two study groups

	Hospital rest (*n* = 110)		Control (*n* = 108)		Significance	
Gestation at delivery (weeks) mean (SD)	38·3	(1·5)	38·2	(1·9)	*P*>0·05	
Length of antenatal hospital stay (days) mean (SD)	22·2	(16·5)	6·5	(7·9)	*P*>0·05	
	n	(%)	*n*	(%)	Odds ratio	(95% CI)
Preterm delivery <37 weeks	13	(11·8)	24	(22·2)	0·48	(0·24–0·97)
Preterm delivery <34 weeks	2	(1·8)	4	(3·7)	0·50	(0·10–2·50)
Development of severe hypertension*						
Primigravidae	4		2		2·27	(0·38–13·34)
Multigravidae						
without chronic hypertension	18		31		0·42	(0·22–0·83)
with chronic hypertension	3		9		0·28	(0·07–1·16)
Total	25	(23)	42	(39)	0·47	(0·26–0·83)
Development of proteinuria						
Primigravidae	11		9		1·96	(0·39–9·83)
Multigravidae						
without chronic hypertension	47		47		0·85	(0·45–1·61)
with chronic hypertension	11		13		1·06	(0·23–4·80)
Total	69	(63)	69	(64)	0·95	(0·55–1·65)
Development of severe proteinuria†						
Primigravidae	4		5		0·72	(0·11–4·61)
Multigravidae						
without chronic hypertension	17		22		0·65	(0·29–1·44)
with chronic hypertension	3		7		0·42	(0·10–1·82)
Total	24	(22)	34	(32)	0·61	(0·32–1·16)
Labour induced	42	(38)	42	(39)	0·97	(0·56–1·67)
Caesarean section	23	(21)	16	(15)	1·51	(0·76–3·02)

*≥ 160/110 mmHg.
†≥3+ Albustix.

bed rest group, otherwise no other statistically significant benefits were observed. This lack of expected beneficial effect may be because, in spite of the decreased risks of developing severe hypertension, the disease process of pregnancy-induced hypertension is not retarded or prevented and the mother and her fetus are still at risk as long as the pregnancy continues.

Table 3. Fetal outcome in the two study groups

	Hospital rest (*n* = 110)		Control (*n* = 108)		Significance	
Birthweight (kg)						
Primigravidae	2·80	(0·51)	2·98	(0·47)	*P*>0·05	
Multigravidae						
without chronic hypertension	3·13	(0·46)	3·06	(0·56)	*P*>0·05	
with chronic hypertension	3·11	(0·62)	3·14	(0·53)	*P*>0·05	
Total	3·08	(0·50)	3·06	(0·54)	*P*>0·05	
	n	(%)	*n*	(%)	Odds ratio	(95% CI)
Infants <2500 g						
Primigravidae	4		2		2·27	(0·38–13·34)
Multigravidae						
without chronic hypertension	5		13		0·34	(0·13–0·91)
with chronic hypertension	2		1		2·49	(0·24–26·04)
Total	11	(10)	16	(15)	0·64	(0·29–1·44)
Small-for-gestational age						
Primigravidae	4		4		1·00	(0·20–5·00)
Multigravidae						
without chronic hypertension	8		10		0·73	(0·27–1·93)
with chronic hypertension	3		1		3·72	(0·47–29·44)
Total	15	(14)	15	(14)	0·98	(0·45–2·11)
Admission neonatal unit	10	(9·1)	12	(11·1)	0·80	(0·29–2·13)

Results are means (SD) or *n* (%) values as appropriate.

This tends to be supported by experimental work on vasoactive agents and intervillous perfusion studies (Everett *et al.* 1978; Whalley *et al.* 1983).

In women with pregnancy-induced hypertension there is a 35–50% reduction in intervillous perfusion, which remains unchanged in spite of the clinical improvements in the hypertension noted with bed rest (Gant & Worley 1980; Worley *et al.* 1985). This again suggests that although bed rest as a therapy has favourable clinical effects on maternal blood pressure it does not affect the underlying disease process.

Acknowledgments

Special thanks to the research midwives Mrs H. Van den Brink, Mrs A. Martin and Mrs J. Maroumahoko, all our medical colleagues and midwifery staff (especially Mrs Matimba and Mrs Newman) who supported the study and Dr Iain Chalmers at the National Perinatal Epidemiology Unit (NPEU) for his continual support and encouragement. Financial support for this work was provided by the University of Zimbabwe and a generous grant from The Sims Black Trust.

References

Butler N. R. & Alberman E. D. (1969) *Perinatal Problems. The Second Report of the 1958 British Perinatal Mortality Survey.* E. & S. Livingstone Ltd, Edinburgh, pp. 47-71.

Chamberlain G. V. P., Philip E., Howlett B. & Masters K. (1978) *British Births 1970,* Vol. 2. *Obstetric Care.* Heinemann, London, pp. 80-107.

Crowther C. A. (1968a) Maternal deaths at Harare Maternity Hospital during 1983. *S Afr Med J* **69**, 180-182.

Crowther C. A. (1986b) A prospective study of hypertension in pregnancy at Harare Maternity Hospital. *Cent Afr J Med* **32**, 175-180.

Davey D. A. & Dommisse J. (1980) The management of hypertension in pregnancy. *S Afr J Med* **58**, 551-555.

Dawson B. (1953) The prevention of eclampsia—an Australian experiment. *J Obstet Gynaecol Brit Commwlth* **60**, 80-84.

Department of Health and Social Security (1986) *Report on Confidential Enquiries into Maternal Deaths in England and Wales. 1979-1981.* HMSO, London.

Dubowitz L. M. S., Dubowitz V. & Goldberg C. (1970) Clinical assessment of gestational age in the newborn infant. *J Paediatr* **77**, 1-10.

Everett R. B., Worley R. J., MacDonald P. L. & Gant N. F. (1978) Effect of prostaglandin synthetase inhibitors on pressor response to angiotensin II in human pregnancy. *J Clin Endocrinol Metab* **46**, 1007-1010.

Friedman E. A. & Neff R. K. (1976) Pregnancy outcome as related to hypertension, oedema and proteinuria. In *Hypertension in Pregnancy,* (Lindheimer M. D., Katz A. & Zuspan F. P., eds), John Wiley and Sons, New York, pp. 13-22.

Gant N. F. & Worley R. J. (1980) Evaluation and management. In *Hypertension in Pregnancy Concepts and Management,* (Gant N. F. & Worley R. J., eds), Appleton Century-Crofts, New York, pp. 107-165.

Hamlin R. H. J. (1952) The prevention of eclampsia and pre-eclampsia. *Lancet* **i**, 64-68.

Hughes T. D. (1956) Antenatal care and the prevention of eclampsia. *Med J Aust* **2**, 48, 52.

Katz D., Baptista J., Azen S. P. & Pike M. C. (1978) Obtaining confidence intervals for the risk ratio in cohort studies. *Biometrics* **34**, 469-474.

Kramer P. D., Constan D., Krzeminiski J., Brondy D. & Martin C. (1986) Hospitalization on the high risk maternity unit. *Gen Hosp Psychiatry* **8**, 33-39.

MacGillivray I. (ed) (1983a) Management of preeclampsia and eclampsia. In *The Hypertensive Diseases of Pregnancy.* W. B. Saunders, London, pp. 227-262.

MacGillivray I. (ed) 1983b) Epidemiology of preeclampsia and eclampsia. In *The Hypertensive Diseases of Pregnancy.* W. B. Saunders, London, pp. 13-22.

Mathews D. D. (1977) A randomized controlled trial of bed rest and sedation or normal activity and non-sedation in the management of non-albuminuric hypertension in late pregnancy. *Br J Obstet Gynaecol* **84**, 108-114.

Powers W. F. & Miller T. C. (1979) Bed rest in twin pregnancy: Identification of a critical period and its cost implications. *Am J Obstet Gynecol* **134**, 23-29.

Whalley P. J., Everett R. B. & Gant N. F. (1983) Pressor responsiveness to angiotensin II in hospitalized primigravid women with pregnancy-induced hypertension. *Am J Obstet Gynecol* **145**, 481-483.

Worley R. J., Everett R. B., MacDonald P. C. & Gant N. F. (1985) Placental clearance of dehydroandrosterone sulfate and pregnancy outcome in three categories of hospitalized patients with pregnancy-induced hypertension (abstract 40). In *Proceedings of the Society of Gynecologic Investigation,* March, 1985.

Received 24 September 1990
Resubmitted 24 June 1991
Accepted 11 July 1991

British Journal of Obstetrics and Gynaecology
January 1992, Vol. 99, pp. 18–22

FETAL AND NEONATAL MEDICINE

Normal amniotic pressure throughout gestation

N. M. FISK
Honorary Lecturer
D. RONDEROS-DUMIT
Research Fellow
Y. TANNIRANDORN
Research Fellow
U. NICOLINI
Senior Lecturer
D. TALBERT
Senior Lecturer in Biomedical Engineering

Royal Postgraduate Medical School
Institute of Obstetrics and Gynaecology,
Queen Charlotte's and Chelsea Hospital, Goldhawk Rd, London
W6 0XG

C. H. RODECK
Professor

Department of Obstetrics and Gynaecology,
University College and Middlesex School of Medicine, University College, London

ABSTRACT

Objective To characterize amniotic pressure (AP) in pregnancies with normal amniotic fluid volume.

Design Observational study, mainly cross-sectional.

Setting Fetal medicine unit within a tertiary referral hospital.

Subjects Patients undergoing transamniotic invasive procedures in whom amniotic fluid volume was subjectively assessed as normal on ultrasound. Those beyond 16 weeks with a deepest vertical pool on ultrasound $<3{\cdot}0$ or $>8{\cdot}0$ cm were excluded. Overall 194 pregnancies were studied on 232 occasions between 7 and 38 weeks gestation.

Interventions Manometry readings referenced to the top of the maternal abdomen were obtained via a fluid-filled line from the needle hub and either connected to a pressure transducer ($n = 190$) or held vertically against a ruler ($n = 42$).

Main outcome measures AP in mm Hg, AP corrected for gestational age (z scores), semi-quantitative ultrasonic indices of amniotic fluid volume, clinical variables.

Results AP in singleton pregnancies increased with advancing gestation ($P<0{\cdot}001$), and the sigmoid-shaped regression curve plateaued in the mid-trimester. AP z scores were not influenced by volume-related phenomena such as twin gestation, the deepest vertical pool, or amniotic fluid index, nor by maternal age, parity, gravidity, fetal sex, or subsequent spontaneous preterm delivery.

Conclusions These findings suggest that AP is not principally determined by intrauterine volume. We speculate that AP, which reflects change in uterine tension as a function of radius, may instead be determined by gestation-specific anatomical and hormonal influences on gravid uterine musculature. A reference range for AP has been constructed for use in amnioinfusion and amnioreduction procedures.

The study of fetal physiology has been greatly facilitated by the access to the intrauterine environment provided by modern invasive procedures. In women undergoing clinically indicated procedures, resting amniotic pressure (AP) has recently been measured by two groups, who reported, albeit on the basis of limited numbers, that AP increases linearly over the last half of gestation (Nicolini *et al.* 1989a; Weiner *et al.* 1989).

AP is high in polyhydramnios (Weiner *et al.* 1989; Fisk *et al.* 1990) and low in oligohydramnios (Nicolini *et al.* 1989a; Fisk *et al.* 1990). It has thus been suggested that the complications of these conditions may be mediated through abnormalities of AP (Nicolini *et al.* 1989b; Fisk *et al.* 1990). We have recently demonstrated that fluid drainage in patients with gross polyhydramnios reduces AP, and speculated that restoration of normal pressure may be an important therapeutic goal in terms of alleviating maternal discomfort, preventing preterm labour and amniorrhexis, and improving fetal blood gas status (Fisk *et al.* 1990). Pressure monitoring has also been advocated during transabdominal amnioinfusion, a procedure recently demonstrated to facilitate diagnosis in mid-trimester oligohydramnios (Fisk *et al.* 1991), to limit the pressure rise (Fisk *et al.* 1990) and thus avoid any risk of amniorrhexis (Gembruch & Hansmann 1988).

The aim of this study was to characterize the development of AP in pregnancies with normal amniotic fluid volume, to examine the extent to which clinical variables influence AP, and to construct a reference range of AP throughout gestation.

Subjects and methods

The study population comprised pregnant women at Queen Charlotte's and Chelsea Hospital between 1987–1990 who were scheduled to undergo a transamniotic invasive procedure, either for diagnostic reasons or during termination of pregnancy in women who consented to participation in an institutionally-sanctioned trial of early-pregnancy sampling techniques. Each had (i) certain menstrual dates confirmed by ultrasound either at the routine 18–20 week examination, or at the time of the procedure if this occurred earlier and (ii) amniotic fluid volume assessed subjectively as normal by ultrasound scan immediately before the procedure. Women were excluded if any of the following were observed during the scan before the procedure: (i) fetal death; (ii) a deepest vertical pool measurement devoid of cord or limbs either $<3{\cdot}0$ or $>8{\cdot}0$ cm in women $\geqslant 17$ weeks gestation, (iii) a fetal abdomi-

Correspondence: Dr N. Fisk, Department of Fetal Medicine, King George V Hospital, Missenden Road, Camperdown NSW 2050, Australia.

nal circumference measurement <5th centile in women ≥18 weeks gestation; (iv) absence of end-diastolic frequencies on pulsed-wave Doppler waveforms of the umbilical artery in women ≥ 18 weeks gestation.

Overall 194 women were enrolled, 186 with singleton, and 8 with twin pregnancies. In the 186 singleton pregnancies, AP was measured at the time of surgical termination for social indications (≤15 weeks) in 40, at cytogenetic amniocentesis (15–18 weeks) in 42, at fetal skin biopsy (15 weeks) in one, during transamniotic fetal blood sampling (FBS) (18–38 weeks) in 92, and at amniocentesis for measurement of optical density (24–33 weeks) in 11 with alloimmunization. The indications for FBS were as follows: rapid karyotyping of ultrasonically detected fetal malformations in 42, assessment of fetal haematocrit or platelet count in 41 with alloimmunization, prenatal diagnosis of β-thalassemia in 3, and cytogenetic study in 6 presenting too late for amniocentesis, or in whom amniocentesis failed or showed mosaicism. In the eight twin pregnancies, AP was measured at termination in one, before selective fetocide in 3 discordant for fetal abnormality, and at FBS in 4 (rapid karyotyping for discordant anomaly in 1, amniotic fluid mosaicism in 1 and maternal age in 2). All gave informed consent to participation in this study which was approved by the institutional ethics committee.

Parity ranged from 0 to 6 (median 1) using international definitions (i.e., parity = no. of deliveries with birthweight ≥500 g or at ≥22 weeks), gravidity from 1 to 8 (median 3), and maternal age from 16 to 43 (mean 30 years). The amniotic fluid index was determined in 128 pregnancies ≥10 weeks using the modification described by Moore & Cayle (1990) to divide the pre-third trimester uterus into four equal quadrants.

All procedures were performed under ultrasound guidance, and pressure measurements were obtained on entry of the needle into the amniotic cavity before the clinical procedure. In those undergoing termination, cervical priming agents were not used, and transabdominal amniocentesis was performed after induction of general anaesthesia with 1·0–1·5 mg/kg propofolol, 0·5–1·0% isoflurane, and a 2 : 1 nitrous oxide/oxygen mixture. In first trimester pregnancies, the amniotic membrane was viewed with ultrasound to ensure that the needle tip was placed within the amniotic cavity rather than the extra-embryonic coelom. Sedation was not used in the remainder. In all except those undergoing cytogenetic amniocentesis, a saline manometry technique was used as described elsewhere (Nicolini *et al.* 1989a). Briefly, a saline filled line was attached at one end to the hub of the needle and at the other to a silicone strain-gauge transducer (EM 750, Elcomatic Ltd, Glasgow, UK). After electronic amplification and display on a meter, the output appeared on a chart recorder (paper speed 5 mm/s). Readings were accepted if stable for 15 s; in the presence of contraction(s), recording was abandoned after 30–45 s if a stable reading could not be obtained. With increasing experience it became apparent that unstable readings could be discerned just as readily from observation of the meter, and thus during the last half of the study, readings were taken directly from the meter, although the same criteria applied. A water manometry system was used in those undergoing cytogenetic amniocentesis for two reasons: firstly, the simpler apparatus was considered less intimidating for these often highly anxious women, and secondly these procedures were done at a different location. When amniotic fluid emerged freely from the needle hub, a sterile plastic line was attached, and the patient's own amniotic fluid aspirated to a height of 15 cm. The 3-way tap at the distal end was then opened to the atmosphere, and the tubing held vertically against a ruler positioned on top of the abdomen. A factor of 0·739 was used to convert readings in cm H_2O to mm Hg.

With both systems, readings were referenced at the top of the maternal abdomen, as previously validated (Fisk *et al.* 1990). Calibration of the electrical system was checked before each reading obtained in mm Hg, by recording the pressure produced by raising the fluid filled line in 6.8 cm increments (5 mm Hg/conversion factor). All readings were made to the nearest 0·5 mm Hg or 0·5 cm of H_2O.

Measurements were repeated after removal of 20–23 ml of amniotic fluid in 22 women undergoing cytogenetic amniocentesis. Serial readings were made on two to four occasions in 27 women being monitored for alloimmunization at 1–12 weekly intervals.

After delivery, details of outcome were obtained from the case notes or from the referring hospital. These were not available in 22 lost to follow up or in 14 continuing pregnancies. Procedure related complications were defined as those occurring within a week of the procedure.

A reference range for singleton pregnancies was calculated from a single reading from 171 of the singleton pregnancies, after exclusion of 7 with unstable recordings and 6 with fetal aneuploidy. Two further pregnancies at 36 and 38 weeks were also excluded in view of the potential for such outliers on the x axis to skew the regression curve. The last reading was used in those with serial recordings to optimize scatter over the three trimesters. The reference range was derived using standard polynomial regression techniques with least squares analysis. The Shapiro–Francia W' test was used to check normality of distribution. A shifted $\log_e$ transformation was required to ensure a normal distribution at each week of gestational age (Royston 1991). After exclusion of heteroscedasticity, the reference range was constructed as 95% data intervals (estimated mean±1·96 SD, where SD = standard deviation) and 95% confidence intervals (CI) for the upper and lower limits determined.

Relations were assessed from the data used in the reference range between amniotic pressure expressed both in mm Hg and z scores (no. of SDs from the mean), and other variables using Pearson and Spearman correlation coefficients for normally and non-normally distributed data as appropriate. Statistical comparisons were made by paired or unpaired *t*-testing as indicated.

Results

Although AP increased significantly with gestational age ($y = 2{\cdot}8 + 0{\cdot}11x$ where y = AP in mm Hg and x = gestational age in weeks, $R^2 = 0{\cdot}17$, $P < 0{\cdot}001$) in the singleton pregnancies, the residuals from this equation were not normally distributed ($W' = 0{\cdot}884$, $P < 0{\cdot}001$). Log_e/constant transformation corrected this ($W' = 0{\cdot}994$, $P > 0{\cdot}9$) and the resulting cubic equation produced a significantly better fit than lower order polynomials ($\log_e(y + 1) = 0{\cdot}12 + 0{\cdot}23x - 0{\cdot}010x^2 + 0{\cdot}00015x^3$, $R^2 = 0{\cdot}19$, $P < 0{\cdot}001$). There was no significant variation in the

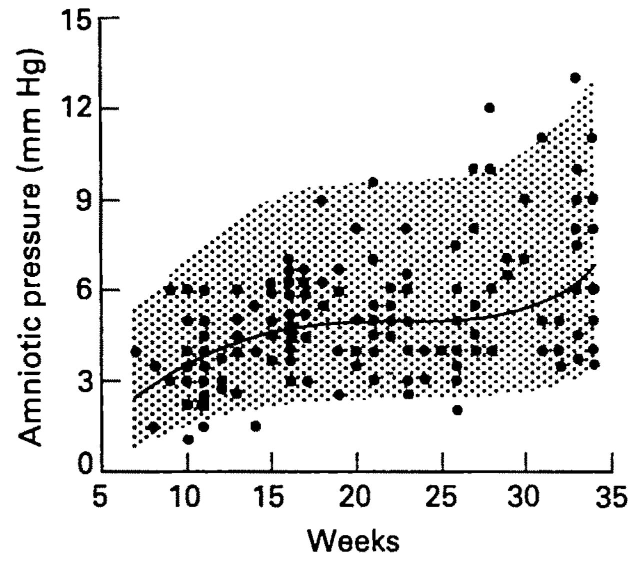


Fig. 1. Amniotic pressure in 171 singleton pregnancies with normal amniotic fluid volume. The line represents the estimated mean ($\log_e (y+1) = 0{\cdot}12 + 0{\cdot}23x - 0{\cdot}010x^2 + 0{\cdot}00015x^3$, $R^2 = 0{\cdot}19$, $P < 0{\cdot}001$ where y = amniotic pressure in mm Hg and x = gestation in weeks) and the shaded area the 95% reference range.

standard deviation of the residuals (heteroscedasticity) over gestational age tertiles. The reference range together with the raw values are shown in Fig. 1. Eight values (4·7%) lay outside the 95% reference range. At the mean gestational age of 20·5 weeks, the 95% CI of the lower and upper limits of the reference range were 2·1 to 2·5 and 8·9 to 10·5 respectively. The upper and lower limits of the reference range are shown in Table 1.

In the women with serial readings (Fig. 2), there was no significant difference between the last AP and the mean of the earlier readings corrected for gestational age (mean difference −0·21 z scores, 95% CI − 0·77 to +0·33, $P = 0{\cdot}4$). The use of the last rather than first serial AP reading in constructing the reference range was further vindicated by the lack of correlation between serial AP, expressed as z scores, and the order of reading (Spearman $r = 0{\cdot}10$).

Table 1. Upper and lower limits of the reference range for amniotic pressure in mm Hg and cm H_2O between 8 and 34 weeks gestation

	Lower limit		Upper limit	
Weeks	mm Hg	cm H_2O	mm Hg	cm H_2O
8	1·1	1·5	6·1	8·2
10	1·5	2·0	7·2	9·7
12	1·8	2·4	8·1	11·0
14	2·0	2·7	8·8	11·9
16	2·2	2·9	9·3	12·6
18	2·2	3·0	9·5	12·9
20	2·3	3·1	9·6	13·1
22	2·3	3·1	9·7	13·1
24	2·3	3·1	9·7	13·1
26	2·3	3·1	9·8	13·3
28	2·4	3·2	10·1	13·6
30	2·5	3·4	10·6	14·3
32	2·8	3·8	11·5	15·6
34	3·2	4·4	13·1	17·7

In singleton gestations, there was no significant correlation between AP expressed as z scores and maternal age (Pearson $r = 0{\cdot}02$), gravidity (Spearman $r = 0{\cdot}11$) or parity (Spearman $r = 0{\cdot}20$). There was no significant difference in AP between nulliparous (mean z score +0·20, 95% CI −0·04 to +0·44) and parous women (mean z score −0·01, 95% CI −0·20 to +0·18). Similarly, there was no significant difference between primigravidae (mean z score 0·12, 95% CI −0·17 to +0·41) and multigravidae (mean z score 0·03, 95% CI −0·14 to +0·21). Figure 3 shows mean AP as a function of parity. AP was similar in pregnancies with male (mean z score 0·26, 95% CI −0·05 to +0·51) compared with with female fetuses (mean z score −0·06, 95% CI −0·21 to +0·33).

Although raw AP was correlated with both amniotic fluid index ($r = 0{\cdot}24$, $P = 0{\cdot}01$) and the deepest pool ($r = 0{\cdot}22$, $P = 0{\cdot}02$), these relations were not significant when AP was expressed in z scores ($P > 0{\cdot}5$ for both). Multiple regression of raw AP on gestational age and amniotic fluid index or deepest pool confirmed that only gestational age had any significant effect on AP ($P = 0{\cdot}01$).

Amniotic pressure was not significantly elevated in twin pregnancies (mean z score 0·37, 95% CI −0·48 to 1·22, $P = 0{\cdot}4$), as shown in Fig. 4. Although three of the twin pregnancies included fetuses with aneuploidy, this was not felt to affect AP, as AP was not altered by fetal aneuploidy in singleton pregnancies (mean z score 0·72, 95% CI −0·58 to +2·03, $P = 0{\cdot}3$).

At a median of 16 weeks, acute drainage of fluid (approximately 10–12% of amniotic fluid volume) (Brace & Wolf 1989) did not alter AP (mean ΔAP 0·12 mm Hg, 95% CI −0·32 to +0·55, $P = 0{\cdot}6$).

After exclusion of procedure related losses, there were no miscarriages, but 12 pregnancies were complicated by spontaneous preterm labour leading to delivery. However, nine of these were patients with Rh alloimmunization, eight of whom underwent multiple procedures, while the remaining three had

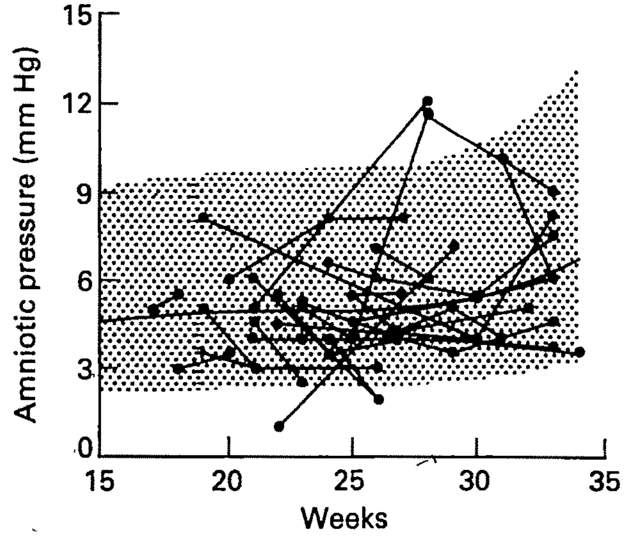


Fig. 2. Amniotic pressure readings in 27 patients with singleton pregnancies in whom serial readings were made. The shaded area represents the 95% reference range.

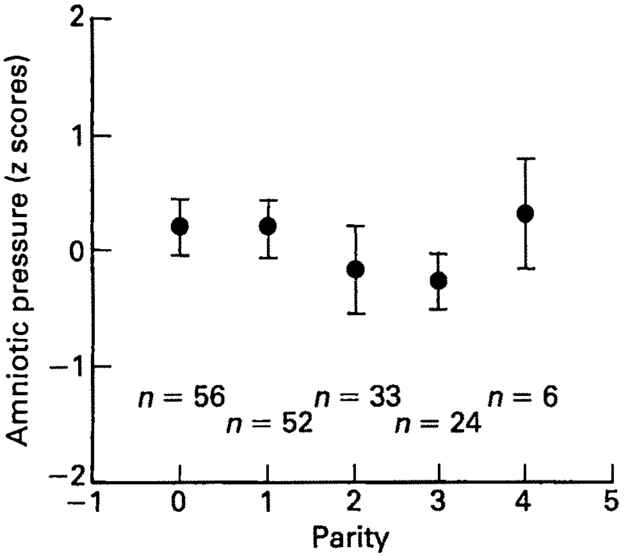


Fig. 3 Mean and 95% confidence intervals for amniotic pressure z scores (SDs from the mean) in relation to maternal parity.

fetal abnormalities. Their mean AP (0·16, 95% CI −0·39 to +0·71) was similar to that in the women delivered at term (0·06, 95% CI −0·16 to +0·28, $P = 0·7$).

Discussion

Although amniotic pressure has been extensively studied over the last four decades, the emphasis has been almost exclusively on its changes with uterine activity (Caldeyro-Barcia & Alvarex 1952; Hellman *et al.* 1957; Hendricks *et al.* 1959; Coren & Csapo 1963; Csapo 1971). The relative inaccessibility of the non-labouring uterus, together with the lack of an agreed reference point, has meant that accurate basal intrauterine pressure measurement has only recently attracted attention.

We have described the normal changes in basal AP throughout gestation. Although some of the pregnancies studied were not strictly normal by virtue of the indication for their invasive procedure, all had ultrasonically normal amniotic fluid volume. Care was taken to ensure stable readings taken during a period of uterine quiescence. It is our experience that the introduction of the needle through the uterine wall may provoke a contraction, while unstable artefactually high readings may occur in anxious women who tense their abdominal muscles. We chose to use isoflurane rather than halothane in those undergoing termination as it has significantly less effect on gravid uterine muscle both in-vivo (Tjeuw *et al.* 1986) and in-vitro (Ghaly *et al.* 1988). Although it remains theoretically possible that the anaesthetic agents used may have affected uterine tone, halogenated anaesthetics have only been shown to affect uterine contractility, not resting tone. Methodologically it may be preferable to use the first rather than last serial value in formulation of the reference range (Royston 1991); however, the lack of difference between last and former readings, and the lack of correlation between AP and the order of reading suggest that this did not materially affect our results. Use of the later gestation readings was necessitated by the relative lack of invasive procedures in third trimester, now that amniocentesis for fetal lung maturity is rarely performed (James *et al.* 1983).

Our results for AP are consistent with preliminary reports of increasing AP with gestation (Nicolini *et al.* 1989a; Weiner *et al.* 1989) and with data obtained at term of basal AP (8–12 mm Hg) in early labour (Caldeyro-Barcia & Alvarez 1952). They are, however, only half as high as those of Weiner *et al.* (1989), who recorded AP after fetal blood sampling and used a variable reference point, the fetal heart. In contrast, we measured AP before other procedures to avoid stimulating contractions, and used a fixed reference point comparable between subjects. There are two components to AP: firstly that due to uterine tension, which according to Pascal's law is equal and uniform within the uterus (Coren & Csapo 1963), and secondly a gravitational component that varies vertically. AP referenced to a variable point will thus vary with the position of that point within the cavity (Fisk *et al.* 1990).

A reference range is now available to determine abnormal amniotic pressures in disorders of amniotic fluid volume and to monitor pressure changes during amnioinfusion and drainage procedures. The mathematical modelling employed in its construction correctly resulted in 5% of values being outside the range. This range is independent of maternal age, parity and gravidity, and allowing for limited numbers studied may also be applicable to twin pregnancies.

The lack of influence of the amniotic fluid index, which reflects amniotic fluid volume (Moore & Cayle 1990), on AP suggests that intrauterine volume is not a primary determinant of AP. Indeed, the lack of effect of drainage on AP in singletons together with the absence of raised pressure in twin gestations supports this contention. Instead it seems that gestational age is the main factor influencing AP. Furthermore the relation of AP to increasing gestation is different from that of amniotic volume, which increases to 22 weeks and does not change significantly thereafter (Brace & Wolf 1989). Our results demonstrate that AP rises in late pregnancy, whereas it had previously been assumed to fall, due to a stable uterine radius and thus volume (Reynolds 1965). Although numerous geometrical shapes have been used to describe the uterine cavity, it may be considered in terms of Laplace's law as a sphere, a mathematical simplification with no significant consequence

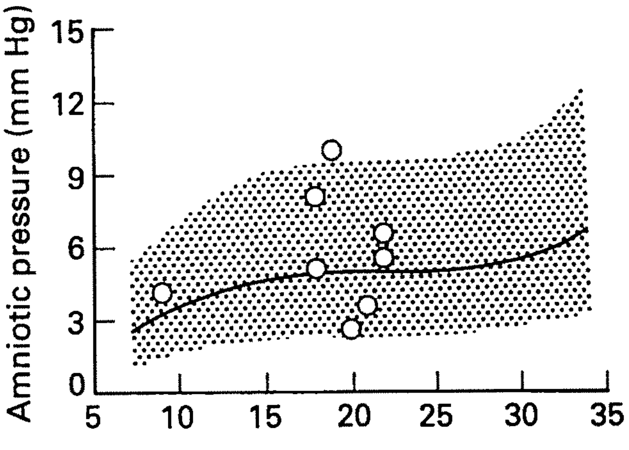


Fig. 4. Amniotic pressure in eight twin pregnancies shown against the reference range for singleton pregnancies.

on results (Coren & Csapo 1963). Thus pressure within the sphere is a function of T/r, where T is the wall tension and r the radius. The initial application of this law to non-living matter held that pressure fell with increasing r. This simple hydrostatic model, however, is complicated with a musculo-elastic structure like the uterus, by the effects of stretch (increasing r) on T. This in turn is modulated by wall thickness, myometrial cell length, and the effects of pregnancy hormones. Furthermore distension is an important stimulus for uterine growth (Reynolds & Kaminensky 1936) and thus further increase in r. Thus the development of AP in pregnancy reflects the relative rate of change of T/r. Our weakly sigmoid shaped curve suggests that AP and thus T relative to r increases more rapidly in the first and third trimesters than in mid-pregnancy. We are unable to deduce T, since uterine radius was not examined in this study. However, a planimetric ultrasound study has suggested that uterine radii increase in a near-linear fashion throughout pregnancy (Gohari *et al.* 1977). We speculate that AP is mediated by gestation-specific anatomical and hormonal influences on gravid uterine musculature.

As uterine distension may be implicated in some causes of preterm labour such as multiple pregnancy and polyhydramnios, we compared AP in pregnancies complicated by spontaneous preterm labour with that of pregnancies progressing to term. The lack of difference suggests that chronic elevation in AP does not precede spontaneous preterm labour, although these findings need to be interpreted with caution in view of the high frequency of multiple procedures and fetal abnormality encountered in this study.

Acknowledgments

N.M.F. was supported by a Joseph Foreman Fellowship from the Royal Prince Alfred Hospital, Sydney, Australia, D.R.-D. by the British Council, and Y.T. by the Anandamahidol Foundation, Chulalongkorn University, Thailand. The authors are grateful to N. MacLachlan, C. Ellis, S. Robson, J. Vaughan and R. Welch for their assistance with the procedures.

References

Brace R. A. & Wolf E. J. (1989) Normal amniotic fluid volume changes throughout pregnancy. *Am J Obstet Gynecol* **161,** 382-388.

Caldeyro-Barcia R. & Alvarez H. (1952) Abnormal uterine action in labour. *J Obstet Gynaecol Br Cwealth* **59,** 646-656.

Coren R. L. & Csapo A. I. (1963) The intra-amniotic pressure. *Am J Obstet Gynecol* **85,** 470-483

Csapo A. (1971) The diagnostic significance of the intrauterine pressure. *Obstet Gynecol Surv* **25,** 403-543.

Fisk N. M., Tannirandorn Y., Nicolini U., Talbert D. G. & Rodeck C. H. (1990) Amniotic pressure in disorders of amniotic fluid volume. *Obstet Gynecol* **76,** 210-214.

Fisk N. M., Ronderos-Dumit D., Soliano A., Nicolini U., Vaughan J. & Rodeck C. H. (1991) Diagnostic and therapeutic transabdominal amnioinfusion in oligohydramnios. *Obstet Gynecol* **78,** 270-278.

Gembruch U. & Hansmann M. (1988) Artificial instillation of amniotic fluid as a new technique for diagnostic evaluation of cases of oligohydramnios. *Prenat Diagn* **8,** 33-45.

Ghaly R. G., Flynn R. J. & Moore J. (1988) Isoflurane as an alternative to halothane for caesarean section. *Anaesthesia* **43,** 5-7.

Gohari P., Berkowitz R. L. & Hobbins J. C. (1977) Prediction of intrauterine growth retardation by determination of total intrauterine volume. *Am J Obstet Gynecol* **127,** 255-260.

Hellman L. M., Tricomi V. & Gupta O. (1957) Pressures in the human amniotic fluid and intervillous space. *Am J Obstet Gynecol* **74,** 1018-1021.

Hendricks C. H. Quilligan E. J., Tyler C. W. & Tucker G. J. (1959) Pressure relationships between the intervillous space and the amniotic fluid in human term pregnancy. *Am J Obstet Gynecol* **77,** 1028-1037.

James D. J. K., Tindall V. R. & Richardson T (1983) Is the lecithin-sphingomyelin ratio outdated? *Br J Obstet Gynaecol* **90,** 995-1000.

Moore T. R. & Cayle J. E. (1990) The amniotic fluid index in normal human pregnancy. *Am J Obstet Gynecol* **162,** 1168-1173.

Nicolini U., Fisk N. M., Talbert D. G., Rodeck C. H., Kochenour N. K., Greco P., Hubinont C. & Santolaya J. (1989a) Intrauterine manometry: Technique and application to fetal pathology. *Prenat Diagn* **9,** 243-254.

Nicolini U., Fisk N. M., Rodeck C. H., Talbert D. G. & Wigglesworth J. S. (1989b) Low amniotic pressure in oligohydramnios—is this the cause of pulmonary hypoplasia? *Am J Obstet Gynecol* **161,** 1098-1101.

Reynolds S. R. M. & Kaminesky S. (1936) Distension, a stimulus for uterine growth in untreated ovariectomized rabbits. *Am J Physiol* **116,** 510-515.

Reynolds S. R. M. (1965) *Physiology of the Uterus* 2nd edition, Hafner, New York, p. 226.

Royston P. (1991) Constructing time-specific reference ranges. *Stat Med* **10,** 675-690.

Tjeuw M. T. B., Yao F. S. & Van Poznak A. (1986) Depressant effects of anesthetics on isolated human gravid and non-gravid uterine muscle. *Chin Med J* **99,** 235-242.

Weiner C. P., Heilskov J., Pelzer G., Grant S., Wenstrom K. & Williamson R. A. (1989) Normal values for umbilical venous and amniotic fluid pressures and their alteration by fetal disease. *Am J Obstet Gynecol* **161,** 714-717.

Received 18 April 1991
Accepted 2 August 1991

British Journal of Obstetrics and Gynaecology
January 1992, Vol. 99, pp. 23–25

FETAL AND NEONATAL MEDICINE

Folate and vitamin B_{12} concentrations in maternal and fetal blood, and amniotic fluid in second trimester pregnancies complicated by neural tube defects

D. L. ECONOMIDES
J. FERGUSON
I. Z. MACKENZIE
Nuffield Department of Obstetrics and Gynaecology.
J. DARLEY
I. I. WARE
Department of Haematology
John Radcliffe Hospital, Headington, Oxford OX3 9DV
M. HOLMES-SIEDLE
Department of Medical Genetics
Churchill Hospital, Headington, Oxford OX3 7LJ

ABSTRACT

Objective To investigate maternal and fetal folate and vitamin B_{12} concentrations in pregnancies affected by neural tube defects (NTD).
Design Measurement of folate and vitamin B_{12} concentrations in amniotic fluid, fetal blood and maternal blood samples in midgestation.
Subjects 32 women undergoing termination of pregnancy at 14–21 weeks gestation for social reasons (n = 24) or for fetuses with neural tube defects (n = 8).
Interventions Fetoscopy before intra-amniotic injection of prostaglandins.
Results In normal pregnancies there was a positive correlation between maternal and fetal serum folate, and the fetal serum and red blood cell folate concentrations were higher than the maternal. There were no differences in amniotic fluid, maternal blood or fetal blood folate concentrations between pregnancies with NTD and normal pregnancies. Although amniotic fluid vitamin B_{12} was lower in pregnancies with NTD, maternal serum vitamin B_{12} concentration was not reduced.
Conclusion In this small group of pregnancies with NTD at mid-gestation there is no evidence to suggest folate or vitamin B_{12} deficiency.

Both vitamin B_{12} and folic acid are utilized for DNA synthesis, and deficiency of either can lead to defective cell proliferation. It has been claimed that fetal neural tube defects (NTDs) can be a consequence of maternal folate or other vitamin deficiencies, and therefore prophylactic maternal vitamin supplementation has been suggested for subsequent pregnancies (Smithells *et al.* 1980; Lawrence *et al.* 1981). Smithells *et al.* (1983) reported a reduction in the recurrence rate of fetal NTDs in women given periconceptional multivitamin supplements and a double-blind randomized controlled trial of folate treatment before conception reported by Lawrence *et al.* (1981) found no recurrence of NTDs in the treated group. The former study was criticized for not being randomized and controlled, and the latter for being too small (Wald 1984); the role of vitamins in the pathogenesis of NTD therefore remains controversial.

To investigate further the possible relations between fetal NTD and maternal vitamin deficiency, folate and B_{12} concentrations in maternal blood, fetal blood and amniotic fluid, were determined in normal pregnancies, and in a small group of pregnancies complicated by NTDs.

Subjects and methods

Fetoscopy and fetal blood sampling was performed in 32 pregnancies before legal abortion by intraamniotic injection of prostaglandins at 14–21 weeks gestation. Twenty-four women (mean gestation 18·9 weeks) were undergoing termination for social reasons under clause two of the Abortion Act 1967. Informed consent was obtained from all the women before fetoscopy. Ethics committee support for the principle of fetal blood sampling at the time of termination had been obtained previously. The fetuses were subsequently confirmed at post-abortion autopsy to be structurally and chromosomally normal. In eight women (mean gestation 17·9 weeks) the fetus was suspected, and subsequently confirmed, to be suffering from either anencephaly or open spina bifida.

Fetoscopy, was performed as described previously (Mackenzie & Maclean 1980). Amniotic fluid (10 ml), as well as fetal blood (1–2 ml) from either the umbilical vein or artery, were obtained under direct vision. In six pregnancies terminated for social reasons, samples from both the umbilical artery and vein were obtained. Maternal venous blood (10 ml) was also collected from an antecubital vein at the time of fetoscopy. None of the women had taken vitamin supplementation immediately before or during this pregnancy.

Serum vitamin B_{12}, serum folate and red blood cell (rbc) folate levels were measured in maternal blood, fetal blood and amniotic fluid. A radioimmunoassay kit (Amersham International, Bucks, UK) was used to measure vitamin B_{12} (intra- and inter-assay coefficients of variation 4·9% and 13·1%, respectively), whilst folate concentrations (intra- and inter-assay coefficients of variation 4·0% and 11·5%, respectively) were determined using a modification of the chloramphenicol resistant lactobacillus method (Water & Mollin 1973). To estimate the rbc folate concentration (inter-assay coefficient of

Correspondence: D. L. Economides.

Table 1. Haematological indices in maternal and fetal blood, and amniotic fluid in pregnancies with neural tube defects (NTD) and in normal pregnancies

	NTD (n = 8)	Normal (n = 24)
Gestation (weeks)	17·9 (16-20)	18·9 (14-21)
Maternal data		
Haemoglobin (g/dl)	11·1 (11·0-13·5)	12·0 (11·5-13·6)
Packed cell volume (%)	38·6 (35-48)	36·9 (31-41)
Mean corpuscular volume (fl)	93·6 (84-99)	93·9 (88-100)
Serum vit B_{12} (ng/l)	205 (85-255)	230 (90-385)
Serum folate (ng/ml)	9·8 (5·1-18)	7·4 (2·6-18)
Red blood cell folate (ng/ml)	435 (270-1055)	400 (245-1000)
Fetal data		
Haemoglobin (g/dl)	11·1 (10·1-11·7)	11·9 (10-13)
Packed cell volume (%)	35·2 (29-34)	35·4 (31-43·8)
Mean corpuscular volume (fl)	141 (133-160)	137 (131-141)
Serum folate (ng/ml)	15·3 (8·8-18)	14·6 (6·8-18)
Red blood cell folate (ng/ml)	960 (580-1450)	970 (400-1340)
Amniotic fluid		
Vit. B_{12} (ng/l)	125 (100-240)*	280 (110-1030)
Folate (ng/ml)	5·5 (4·3-18)	3·6 (1·6-14·4)

*P<0·01. Results are medians (range) values.

variation 9%), whole blood was initially diluted 1 in 20 and then assayed. Because of fetal blood volume limitations, it was not possible to measure B_{12} in the umbilical blood samples. The maternal and fetal haemoglobin, haematocrit and mean corpuscular volume were also measured using the Coulter 'S'-Plus IV counter (Coulter Electronics, UK).

Results were analyzed using the Statistical Package for personal computers, by P. Royston. Correlations between maternal, fetal and amniotic fluid values were determined by the Spearman rank method. Paired maternal and fetal results were compared using a paired t-test. The Mann-Whitney U-test was used to establish any significant differences between the NTD and normal pregnancies.

Results

In normal pregnancy, maternal and fetal haemoglobin, and maternal and fetal serum folate concentrations did not appear on a scatter plot to be associated with gestation between 14 and 21 weeks. Both fetal serum folate (t = 4·2, P<0·0001) and rbc folate (t = 7·18, P<0·0001) concentrations were significantly higher than the maternal concentrations (Table 1), but folate concentration was significantly lower in amniotic fluid than in fetal (t = 7·58, P<0·0001) or maternal (t- = 3·05, P<0·01) samples. In paired umbilical blood samples, there were no significant differences in rbc folate or serum folate concentrations between artery and vein blood samples. Table 2 shows the correlations between maternal, fetal and amniotic fluid folate or vitamin B_{12} concentrations. There are significant correlations for all indices, except for maternal and fetal rbc folate concentrations.

Table 2. Correlations between maternal blood, fetal blood and amniotic fluid concentrations of folate or vitamin B_{12} in normal pregnancies

	r	n	P value
MS folate *vs* FS folate	0·61	23	0·01
M rbc folate *vs* F rbc folate	0·21	21	>0·05
MS folate *vs* AF folate	0·63	18	0·01
FS folate *vs* AF folate	0·48	19	0·05
MS B_{12} *vs* AF B_{12}	0·89	18	0·001
MS B_{12} *vs* MS folate	0·06	23	>0·05
MS B_{12} *vs* M rbc folate	−0·11	21	>0·05
AF B_{12} *vs* AF folate	0·02	23	>0·05

Abbreviations: AF, amniotic fluid; MS, maternal serum; FS, fetal serum; rbc, red blood cells, B_{12} vitamin B_{12}.

In Table 1 the values in normal and NTD pregnancies are shown. In NTD pregnancies there was a significant decrease in amniotic fluid vitamin B_{12} compared with normal pregnancies (P<0·01), but there were no significant differences in the other indices.

Discussion

The concentrations of serum and rbc folate from the relatively undisturbed human fetus at 14–21 weeks gestation are reported. The concentration of serum folate in the mid-trimester fetus is similar to the neonatal serum folate concentration measured in cord blood after vaginal delivery at term (Giugliani *et al.* 1985a). The positive correlations observed in the pregnancies with normal fetuses between maternal serum, fetal serum and amniotic fluid folate concentrations imply a common origin for folate. Fetal serum and rbc folate concentrations were much higher than maternal, a similar relation to that found at term (Giugliani *et al.* 1985a), suggesting that folate is transferred against a concentration gradient from mother to fetus. However, in the small number of pregnancies examined we could not demonstrate a significant umbilical arterio-venous concentration gradient. The high concentration of serum folate might also be due in part to the strong affinity of folic acid to a binding factor in fetal serum (Kamen & Caston, 1975).

In mid-trimester pregnancies, amniotic fluid vitamin B_{12} was higher than the maternal serum vitamin B_{12} concentration, and there was a significant positive correlation between the two, suggesting that there is transplacental transfer of this vitamin. In infants born at term, serum vitamin B_{12} has been shown to be closely related to the maternal and intervillous blood levels, and to be 2·3 times higher on average than the maternal levels (Giugliani *et al.* 1985b). Therefore, it appears that vitamin B_{12}, like folate, is transferred to the fetus against a concentration gradient but the mechanism for this is unclear. Although amniotic fluid folate concentration is lower than the maternal serum concentration, the opposite situation exists for amniotic fluid vitamin B_{12}.

The folate concentrations in maternal blood, fetal blood or amniotic fluid in the small group of pregnancies with NTD examined were not different from normal pregnancies, suggesting that, at least in mid-gestation, folate deficiency in pregnancies with NTD is unlikely. We acknowledge, however, that our results should be interpreted with caution since the pregnancies were in mid-gestation and organogenesis occurs in the first trimester. Gardiki-Kouidou & Seller (1988) also demonstrated that amniotic fluid folate was not reduced in pregnancies with NTD. In addition, in a large study of maternal serum folate in various stages of pregnancy, including the first trimester, there was no association between low serum folate and teratogenesis (Hall 1972). Also, Molloy *et al.* (1985) found no significant difference in maternal serum folate concentration between pregnancies with NTD and normal controls. In contrast, in non-pregnant women who had had a pregnancy with NTD, mean rbc folate concentration was found to be low, despite adequate dietary folate intake, suggesting that there might be an inherited disorder of folate metabolism in these women (Yates *et al.* 1987).

The amniotic fluid vitamin B_{12} concentration was significantly lower in pregnancies with NTD than in normal pregnancies, and this has also been demonstrated by Gardiki-Kouidou & Seller (1988), but since maternal vitamin B_{12} concentration was not reduced, dietary deficiency of this vitamin is unlikely to be implicated in the pathogenesis of NTD. Furthermore, the reduced amniotic fluid vitamin B_{12} levels (Gardiki-Kouidou & Seller 1988) and the increased amniotic fluid transcobalamin levels (Magnus *et al.* 1986), associated with normal pregnancy in women who had had a previous pregnancy with NTD, suggests that the predisposition to NTD might be genetic rather than dietary.

Our results thus suggest that, in mid-gestation, vitamin B_{12} or folate do not appear to be deficient in pregnancies complicated by NTD, although vitamin metabolism in these pregnancies may not be normal since amniotic fluid vitamin B_{12} concentration is reduced. It would be of great interest to determine whether vitamin B_{12} concentration is reduced in the blood of fetuses with NTDs.

Acknowledgment

We would like to thank Pat Yudkin for her statistical advice, and the physicians for referring the patients.

References

Gardiki-Kouidou P. & Seller M. J. (1988) Amniotic fluid folate, vitamin B_{12} and transcobalamins in neural tube defects. *Clin Genet* **33,** 441-448.

Giugliani E. R., Jorge S. M. & Gonsalves A. L (1985a) Serum and red blood cell folate levels in parturients, in the intervillous space of the placenta and in full-term newborns. *J Perinat Med* **13,** 55-59.

Giugliani E R , Jorge S. M. & Gonsalves A. L. (1985b) Serum vitamin B_{12} levels in the parturients, in the intervillous space of the placenta and in full-term newborns and their interrelationships with folate levels. *Am J Clin Nutr* **41,** 330-335.

Hall M. H. (1972) Folic acid deficiency and congenital malformations. *J Obstet Gynaecol Br Commonw* **79,** 159-161.

Kamen B. A. & Casten J D (1975) Purification of folate binding factor in normal umbilical cord serum. *Proc Nat Acad Sci* **72,** 4261-4264.

Lawrence K. M., James N., Miller M. H., Tennant G. B. & Campbell H. (1981) Double blind randomized controlled trial of folate treatment before conception to prevent recurrence of neural tube defects.` *Br Med J* **282,** 1509-1511.

Mackenzie I. Z. & Maclean D. A. (1980) Pure fetal blood from the umbilical cord obtained at fetoscopy. experience with 125 consecutive cases. *Am J Obstet Gynecol* **138,** 1214-1218.

Magnus P., Magnu E. M. & Berg K. (1986) Increased levels of apotranscobalamins I and II in amniotic fluid from pregnant women with previous neural tube defect offspring. *Clin Genetics* **30,** 167-172.

Molloy A. M., Kirke P., Hillary I., Weir D. G. & Scott J. M. (1985) Maternal serum folate and vitamin B_{12} concentrations in pregnancies associated with neural tube defects. *Arch Dis Child* **60,** 660-665.

Smithells R. W., Sheppard S., Schorah C. J., *et al.* (1980) Possible prevention of neural tube defects by periconceptional vitamin supplementation. *Lancet* **i,** 339-340.

Smithells R. W., Nevin N. C., Seller M. J., *et al* (1983) Further experience of vitamin supplementation for prevention of neural tube recurrences. *Lancet* **i,** 1027-1031.

Yates J. R. W., Ferguson-Smith M. A., Shenkin A., Guzman-Rodriguez R., White M. & Clark B. J. (1987) Is disordered folate metabolism the basis for the genetic predisposition to neural tube defects? *Clin Genetics* **31,** 279-287.

Wald N. J. (1984) Neural tube defects and vitamins: the need for a randomized clinical trial. *Br J Obstet Gynaecol* **91,** 516-52.

Water A. H. & Mollin D. L. (1973) Diagnosis of folate deficiency. *Association of Clinical Pathologists Broadsheet* **79,** 1-7

Received 18 February 1991
Accepted 14 May 1991

British Journal of Obstetrics and Gynaecology
January 1992, Vol. 99, pp. 26–31

FETAL AND NEONATAL MEDICINE

Fetal acidaemia, the cardiotocograph and the T/QRS ratio of the fetal ECG in labour

NEIL A. MACLACHLAN
JOHN A. D. SPENCER
KATE HARDING
SABARATNAM
ARULKUMARAN

Institute of Obstetrics and Gynaecology, Royal Postgratuate Medical School, University of London, Queen Charlotte's and Chelsea Hospital, Goldhawk Road, Chiswick, London W6 0XG

ABSTRACT

Objective To relate the T/QRS ratio of the fetal electrocardiogram (ECG) to the cardiotocogram (CTG) and fetal pH during labour.
Design Prospective data collection from selected monitored labours.
Setting A postgraduate teaching hospital delivery suite.
Subjects 113 women in labour at term.
Main outcome measures Correlation of fetal T/QRS ratio values with pH values at the time of fetal blood sampling and at birth (umbilical artery blood). Comparison of the predictive values of raised T/QRS ratio and a pathological CTG for fetal acidaemia.
Results Complete data sufficient for analysis was available for 51 fetal scalp blood samples and 93 umbilical artery pH samples. The median (range) of T/QRS ratio values before birth of 88 babies not requiring admission to the neonatal unit was 0·13 (0·00–0·32) with a 97·5th centile value of 0·28. T/QRS ratios did not correlate with fetal scalp pH values. Fetal scalp acidaemia (pH<7·20) was detected with rates of 50 and 13% respectively by a pathological CTG and by a T/QRS ratio above 0·28, the positive predictive values being 40% and 50%, respectively. There was a significant correlation between increasing T/QRS ratio and falling pH. Detection rates (sensitivities) for umbilical artery acidaemia (pH <7·12) were 76% and 29% whereas positive predictive values were 38% and 71% respectively for a pathological CTG and a T/QRS ratio above 0·28.
Conclusion A raised T/QRS ratio (>0·28) had a considerably lower detection rate for fetal acidaemia during labour than a pathological CTG.

The ability to make an accurate assessment of fetal well-being during labour from the cardiotocogram (CTG) has recently been questioned (Murphy *et al.* 1990). Fetal blood sampling, whilst necessary to minimize the increased rate of operative intervention associated with fetal heart rate (FHR) abnormalities seen on the CTG (Thacker 1991), is practised in less than 50% of consultant units in the UK (Wheble *et al.* 1989). Reflex FHR decelerations indicate adaptive cardiovascular adjustments to hypoxia in fetal sheep (Itskovitz *et al.* 1982) which include maintaining or increasing blood supply to the brain, heart and adrenals (Cohn *et al.* 1974). Artery blood pH may remain normal (Parer *et al.* 1980). Severe hypoxaemia stimulates catecholamine release (Gu *et al.* 1985) and associated myocardial anaerobic glycogenolysis changes the potassium gradient across the myocardial cell membrane producing ST elevation and a raised T/QRS ratio (Rosen *et al.* 1984). Analysis of the fetal electrocardiogram (ECG) together with the FHR on the CTG has been suggested as a possible means by which the prediction of fetal acidaemia may be improved (Jenkins *et al* 1986; Arulkumaran *et al.* 1990) and a new monitor has been designed to provide on-line calculation of the T/QRS ratio from the fetal ECG during labour for display on the CTG (Rosen & Lindecrantz 1989).

This study was designed to compare the predictive values of a raised T/QRS ratio with a pathological CTG for fetal acidaemia during labour and at delivery and to relate the T/QRS ratio to pH and to neonatal condition.

Subjects and methods

A total of 113 women in labour with a singleton fetus presenting by the head at term (37–42 weeks) was included in the study. Pregnancies with an abnormal CTG were selected preferentially even though the abnormality did not always persist. The FHR was monitored using a standard scalp electrode (Copeland, Surgicraft Ltd, Redditch, UK) and an FM6 (Oxford Sonicaid, Chichester, Sussex, UK) or HP 8031 (Hewlett Packard, Uxbridge, Middlesex, UK) fetal monitor. The fetal ECG was taken from the same scalp electrode and maternal leg plate for on-line calculation and recording of the T/QRS ratio by a STAN monitor (Cinventa, Gothenberg, Sweden). The T/QRS ratio data were not used for clinical management. The study

Correspondence: John A. D. Spencer, Senior Clinical Lecturer and Consultant, Department of Obstetrics and Gynaecology, University College and Middlesex School of Medicine, University College London, 86–96 Chenies Mews, London, WC1E 6HX, UK.

was approved by the hospital ethics committee and all women gave informed consent.

The method of signal processing by the STAN monitor has been described (Rosen & Lindecrantz 1989). Ten values of the fetal T/QRS ratio were averaged and printed onto paper at approximately 2-min intervals. The mean of three such average ratios (at least 6-min of record) was taken as representative of the signal before each fetal blood sample (FBS) and before delivery. Waveforms included for analysis were within 10 min of the FBS or within 30 min of delivery. Signals with excessive 50 Hz noise, a wandering baseline or those without a clear P wave were not considered for analysis.

An FBS was collected when clinically indicated, usually to assess FHR changes. All scalp samples were collected with women in the left lateral position and only first samples were used in the analysis. Umbilical artery blood was collected into a preheparinized syringe from a double-clamped section of cord for immediate acid-base analysis. The pH and base deficit was obtained using a standard blood gas analyser (ABL 30, Radiometer, Copenhagen, Denmark), and extracellular base deficit was derived from a nomogram (Siggaard-Andersen 1971). The CTG during the 30 min before each FBS and before delivery was classified as normal, suspicious or pathological (FIGO News 1987).

Patient data and information regarding outcome were collected, including mode of delivery, birthweight, Apgar scores and admission to the neonatal unit. A normal range of values for the T/QRS ratio was determined from those cases where the baby did not require admission to the neonatal unit.

Predictive values (Wald & Cuckle 1989) of the CTG and T/QRS ratio for fetal acidaemia during the first stage of labour (FBS pH <7·20) and at birth (umbilical artery pH <7·12) were compared. T/QRS ratio values were correlated with fetal pH values using the Spearman equation. Wilcoxon's signed rank test for unpaired data and the χ^2 test were used to compare different groups, the 5% significance level was used.

Results

CTG and T/QRS ratio before delivery

Umbilical cord blood analysis with an interpretable CTG trace within 30 min of delivery was available for 93 labours. These labours were grouped according to their CTG classification and are shown in Table 1. As can be seen, there are remarkably few differences between the three groups, particularly with respect to duration of labour and outcomes such as caesarean section rate and birthweight. However, the groups with suspicious and pathological CTGs had significantly higher rates of fetal blood sampling ($\chi^2 = 51{\cdot}4$, df = 2, $P<0{\cdot}001$) and significantly lower median umbilical artery pH values ($P<0{\cdot}03$ and $<0{\cdot}001$ respectively) compared with the group with normal CTGs.The median T/QRS ratio before delivery was not significantly different between any of the three FHR groups.

The median umbilical artery pH in these 93 pregnancies was 7·21 (range 6·97–7·43, 2·5th centile 7·04). All pH values below 7·01 had an extracellular base deficit of ≥12 mmol/l indicating metabolic acidaemia. Seventeen fetuses (18%) were

Table 1. Description of labours with T/QRS ratio and umbilical artery pH data at delivery, grouped according to the FIGO CTG classification

	Normal (*n* = 28)	Suspicious (*n* = 31)	Pathological (*n* = 34)
Age (years) mean (SD)	28 (4·8)	27 (5·1)	29 (5·3)
Gestation, (weeks) mean (SD)	39 (1·4)	39 (1·4)	39 (1·7)
Primipara, *n* (%)	21 (75)	23 (80)	23 (74)
Spontaneous labour, *n* (%)	19 (67)	16 (57)	21 (68)
Duration labour (h), median	10	9	10
range	(5–19)	(4–16)	(3–19)
Analgesia, *n* (%)			
None	9 (32)	8 (25)	7 (23)
Pethidine	2 (7)	5 (25)	5 (17)
Epidural	17 (61)	18 (57)	22 (64)
Fetal blood sampling, *n* (%)	2 (7)	11 (35)*	18 (54)*
Pre-delivery T/QRS ratio, median	0·12	0·16	0·16
range	(0·00–0·28)	(0·05–0·32)	(0·03–0·32)
T/QRS ratio > 0·28, *n* (%)	0	4 (13)	3 (9)
Mode of delivery, *n* (%)			
Spontaneous	16 (57)	13 (42)	14 (41)
Operative vaginal	8 (29)	14 (39)	14 (41)
Caesarean section	4 (14)	4 (15)	6 (16)
Birthweight (kg), mean (SD)	3·3 (0·64)	3·4 (0·50)	3·2 (0·49)
Umbilical artery (UA) pH, median	7·26	7·21†	7·15*
range	(7·17–7·43)	(6·97–7·36)	(6·97–7·42)
UA pH<7 12, *n* (%)	2	4 (13)	13 (38)*
Apgar score <7			
At 1 min, *n* (%)	4 (14)	4 (15)	9 (29)
At 5 min, *n* (%)	0	0	1 (3)
Neonatal unit admission, *n* (%)	0	1 (3)	4 (12)

Significance of difference compared with normal CTG group *$P<0$ 001, †$P<0{\cdot}03$.

Table 2. Predictive values of pathological CTG and raised T/QRS ratio before delivery for umbilical artery (UA) acidaemia (pH<7·12)

	Pathological CTG	Raised T/QRS (>0·28)
UA pH<7·12 (n = 17)	13 (76%)	5 (29%)
UA pH≥7·12 (n = 76)	21 (28%)	2 (3%)
Prevalence of acidaemia (%)	18	18
Detection rate (sensitivity) (%)	76	29
Specificity (%)	72	97
False negative rate (%)	7	14
False positive rate (%)	62	29
Positive predictive value (%)	38	71
Odds of being acidaemic given an abnormal result	3:5	5:2

acidaemic as defined by an umbilical artery pH <7·12 (1 SD below the mean of 7·20) and the median T/QRS ratio of this group (0·21) was significantly higher than the median T/QRS ratio of the non acidaemic fetuses (0·13, P<0·001). Thirteen of the 17 acidaemic fetuses had a metabolic acidaemia; three with a suspicious and ten with a pathological CTG. A further three acidaemic fetuses also had a pathological CTG which therefore had a positive predictive value of 38% for this degree of acidaemia (Table 2). All fetuses with a normal FHR before birth had a cord artery pH> 7·11. The frequency of acidaemia was greatest in the group with pathological CTGs (χ^2 = 15·93, df = 2, P<0·001) as indicated in Table 1.

The correlation between the range of values for T/QRS ratio before delivery and all umbilical artery pH values (Fig. 1) was significant (r = 0·35, Spearman P<0·001). A normal range for the T/QRS ratio was derived from 88 fetuses that did not require admission to the neonatal unit after birth. The median was 0·13 (range 0·00–0·32, 97·5th centile 0·28). Of all 93 fetuses, seven had a T/QRS ratio ≥0·28 before delivery. The median pH of this group was 7·09 (range 7·02–7·23) and the median extracellular base deficit was 11 mmol/l (range 6·0–15·0 mmol/l). None was admitted to the neonatal unit. Three had pathological CTG traces and were acidaemic while the other four had suspicious CTG traces, two of which were acidaemic. Thus the positive predictive value of a raised T/QRS ratio for acidaemia at birth was 71% but the detection rate (sensitivity) was only 29% (Table 2). A T/QRS ratio of ≥0·25 identified 41% of acidaemic fetuses with a positive predictive value of 54% (Kappa 0·37).

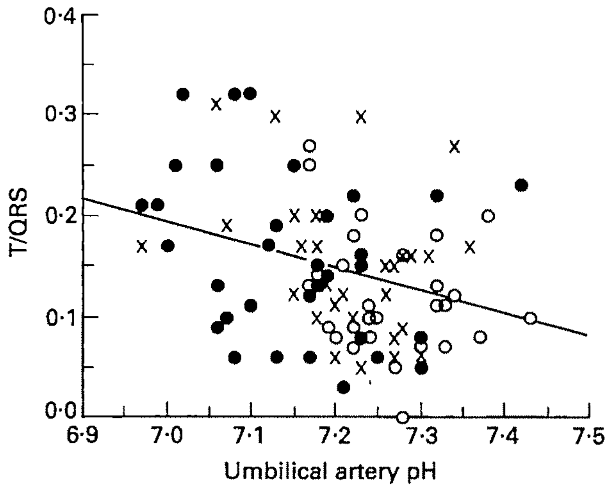


Fig. 1. Correlation between the T/QRS ratio of the fetal ECG before delivery and umbilical artery pH (n = 93, r = 0·349, P<0·001). CTG classification (FIGO) ○ = normal, × = suspicious, ●= pathological.

Neonatal condition

One baby with a suspicious CTG and four with a pathological CTG required admission to the neonatal unit. However, none of them had clinical signs of severe birth asphyxia. Four had metabolic acidaemia and all five had T/QRS ratios <0·28. Two were small for gestational age and each had an umbilical artery pH <7·00. One of the babies was born by caesarean section because of clinical signs of abruption (see Fig. 2). Another caesarean section was performed for abruption and the fourth acidaemic baby was born by forceps when the mother had an eclamptic seizure in the second stage of labour. The non-acidaemic baby was septic and required antibiotics. None had abnormal neurological features and all were normal and thriving on leaving hospital. Full details of these babies are listed in Table 3. All other acidaemic fetuses were well at birth.

FHR and T/QRS ratio before fetal blood sampling in labour

Thirty-one labours described in Table 1, and a further 20 women with missing delivery data (uninterpretable T/QRS ratio before delivery, last ratio more than 30 min before delivery, no umbilical artery pH) had fetal blood sampling performed during labour. The median pH value of all first scalp blood samples was 7·28 (range 7·06–7·39) and eight (16%) were acidaemic (pH<7·20, 1 SD below the mean of 7·27). There were significant differences between the median pH value of the normal CTG group (n = 11, median 7·31, range 7·29–7·36) and values for the suspicious (n = 30, median pH 7·28, range 7·13–7·39, P<0·01) and pathological (n = 10,

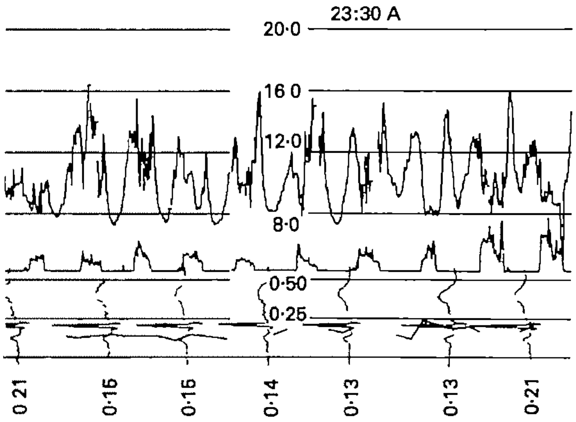


Fig. 2. Record of an infant admitted to neonatal unit (no. 1, Table 3) showing a pathological CTG and normal T/QRS ratio values in the second stage, just before delivery. Averaged ECG waveform samples and derived T/QRS ratio values can be seen plotted at approximately 2 min intervals. The trend in T/QRS ratio is plotted along the lower part of the record. Paper speed 1 cm/min.

Table 3. Details of the five babies admitted to the neonatal unit

Infant no.	Gestation (weeks)	CTG	T/QRS ratio	UA pH	BE (ecf) (mmol/l)	Weight (g)	Outcome (days in hospital)
1	39	Path	0·21	6·97	−16·0	2200	SVD, observation, (2)
2	39	Path	0·21	6·99	−14·0	1700	CS, oesophageal atresia, (12)
3	38	Path	0·25	7·01	−13·0	3000	OVD, rhesus, RDS, (7)
4	37	Path	0·17	7·00	−12·0	2400	OVD, diazepam, (2)
5	40	Susp	0·05	7·23	− 7·0	4500	SVD, septic (2)

Abbreviations: CTG = cardiotocogram: path = pathological, susp = suspicious (FIGO 1987). UA = umbilical artery; BE (ecf) = base excess in the extracellular fluid; SVD = spontaneous vaginal delivery, OVD = operative vaginal delivery, CS = caesarean section; RDS = respiratory distress syndrome.

median pH 7·22, range 7·06–7·28, $P = 0·0001$) CTG groups. Four (detection rate 50%) acidaemic fetuses were associated with a pathological CTG which had a positive predictive value of 40% (Table 4). All normal, and 26 (88%) suspicious CTG traces were associated with a scalp pH value of 7·20 or more.

The median T/QRS ratio at the time of fetal blood sampling was 0·15 (range 0·00–0·37, 97·5th centile 0·29). The median T/QRS ratios of the normal (0·17), suspicious (0·14) and pathological (0·13) CTG groups were not significantly different. The T/QRS ratio was above 0·28 in two labours; one with a pathological CTG had a scalp pH value of 7·06 (detection rate 13%) and one with a normal CTG had a scalp pH of 7·32. All other T/QRS ratios were less than 0·26. The positive predictive value of a raised T/QRS ratio for scalp acidaemia was 50% (Table 4). All eight fetuses with a pH below 7·20 had respiratory acidaemia. The median T/QRS ratio for this group was 0·20 which was significantly higher than that for non-acidaemic fetuses (median 0·14, $P<0·02$). There was no correlation between all first scalp pH values and the preceding T/QRS ratio (Fig. 3). However, pH values of 7·25 or less showed a strong correlation with increasing T/QRS ratios (r 0·71, $P<0·001$) and none of these cases had a normal CTG.

Discussion

In the present study, the mean umbilical artery pH was 7·20 (SD 0·09) which agrees closely with previously reported mean (SD) values: 7·20 (0·08) (Sykes *et al.* 1982), 7·23 (0·07) (Eskes *et al.* 1983) and 7·22 (0·08) (Josten *et al.* 1987). It is also representative of our own total population (mean pH 7·22, SD 0·08) derived from 247 consecutive deliveries studied in 1988 (Wheble & Spencer, unpublished data). We also found that 1 SD below the mean scalp pH (7·19) was similar to the lower limit of normal pH (7·20) recommended for use in clinical practice (Kubli *et al.* 1969; Beard *et al.* 1971; Tejani *et al.* 1975). Mean (SD) values for the T/QRS ratio of the fetal ECG have been variously reported as 0·20 (SD 0·11) (Lilja *et al.* 1985) and 0·15 (SD 0·05) (Lilja *et al.* 1988) and 0·10 (SD 0·05) (Newbold *et al.* 1989) during human labour. The normal range in fetal sheep was reported below 0·3 (Greene *et al.* 1982) and hypoxia in fetal sheep produced a significant increase to values between 0·33 and 2·25 (Greene *et al.* 1982, Rosen *et al.* 1984), depending upon the level of catecholamine surge. The position of the ECG electrodes in fetal sheep may also contribute to the higher ratio. We found a relation between umbilical artery pH values and the T/QRS ratio but the range of T/QRS ratio values did not exceed 0·32. Median values of 0·13 (cord) and 0·15 (scalp) in our study were similar to the normal value (0·20) reported by Lilja *et al.* (1988), who used the same equipment, and the value reported for normal subjects (0·10) by Newbold *et al* (1989) whose analysis technique used the pre P-wave region rather than the PR segment as a reference baseline (Newbold *et al.* 1991).

Table 4. Predictive values of a pathological CTG and a raised T/QRS ratio prior to first fetal blood samples for fetal scalp acidaemia (pH<7·20)

	Pathological CTG	Raised T/QRS (>0·28)
Fetal scalp pH<7·20 (n = 8)	4 (50%)	1 (13%)
Fetal scalp pH ≥7·20 (n = 43)	6 (14%)	1 (2%)
Detection rate (sensitivity) (%)	50	13
Specificity (%)	86	98
False negative rate (%)	10	14
False positive rate (%)	60	50
Positive predictive value (%)	40	50
Odds of being acidaemic given an abnormal result	2:3	1:1

We selected labours at risk of fetal distress in order to compare the predictive values of a pathological CTG and raised T/QRS ratio for fetal acidaemia. Thus, the distributions of the different CTG groups are not representative of the population

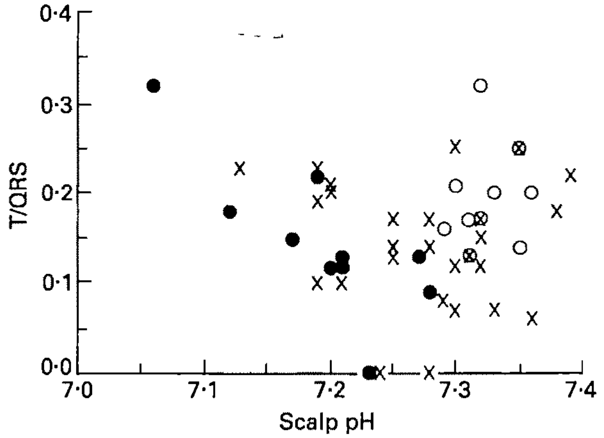


Fig. 3. Correlation between the T/QRS ratio of the fetal ECG before fetal blood sampling and fetal scalp pH (n = 51, r = 0·065, P = not significant). CTG classification (FIGO) ○ = normal, × = suspicious, ● = pathological.

as a whole. The CTG, classified according to the FIGO guidelines, correlated well with umbilical artery pH; fetuses with pathological traces were significantly more acidaemic. The positive predictive values of 38% (cord) and 40% (scalp) for acidaemia are in accordance with other studies relating the CTG to fetal pH (Tejani *et al.* 1975, Young *et al.* 1980, Heinrich *et al.* 1982).

Although the T/QRS ratio correlated with umbilical artery pH and the predictive value of a raised ratio for acidaemia at this time was twice that of a pathological CTG, the detection rate was less than half. At the time of fetal blood sampling the positive predictive value of a raised T/QRS ratio was similar to that of a pathological CTG for scalp acidaemia but the detection rate was again lower, being only one fourth that of a pathological CTG. As expected, there were significantly more fetal blood samples in the abnormal CTG groups but there were no significant differences in mode of delivery suggesting that many of the pathological CTG group did not have significant acidaemia. Whilst the suspicious and pathological CTG groups had significantly lower mean umbilical artery pH values compared with the normal CTG group, there was considerable overlap in the ranges of umbilical pH values (from 6·9 to 7·4). This is in line with the findings of Sykes *et al.* (1982) and Murphy *et al.* (1990) that CTG interpretation in clinical practice is inaccurate and does not prevent acidaemia at birth.

Elevation of the T/QRS ratio represents a change to anaerobic myocardial metabolism (Greene *et al* 1982) secondary to beta-adrenergic stimulation (Rosen *et al.* 1984) and offers a means by which myocardial adaptation to hypoxia might be identified (Rosen 1986). In our study the fetuses with respiratory acidaemia (scalp blood) had a significantly higher mean value of T/QRS ratio (0·20 *vs.* 0·14) compared with non acidaemic fetuses, yet they were born in good clinical condition. Fetuses born with umbilical artery metabolic acidaemia had a higher mean T/QRS ratio (0·21 *vs* 0·13) compared with non-acadaemic fetuses before birth and this is consistent with a trend of increasing T/QRS ratio with acidaemia, although there seemed to be no significant difference between respiratory and metabolic acidaemia. Interpretation of CTG changes might be improved if those without an associated rise in the T/QRS ratio could be reliably discounted as false positives. The question of a 'gold standard' outcome against which it would be appropriate to determine the upper limit of a normal range remains unresolved. Clearly, acidaemia does not correlate well. In addition, the results of a recent neurodevelopmental outcome follow-up study suggested that fetal acidaemia may represent the ability of the fetus to adapt successfully to intrapartum hypoxia (Dennis *et al.* 1989). Metabolic acidaemia at birth has been shown to be poorly predictive of subsequent neurological function (Ruth & Raivio 1988; Fee *et al.* 1990). The range of values for T/QRS ratio in our study was not associated with significant clinical birth asphyxia (CTG abnormalities, umbilical acidaemia, resuscitation at birth and abnormal neonatal neurological signs, Murphy *et al.* 1990) and it remains to be seen whether this clincal outcome is associated with higher values of T/QRS ratio.

Four of our five admissions to the neonatal unit had pathological CTG traces and metabolic acidaemia: all had a T/QRS ratio below 0·28 and none of them had birth asphyxia, as was also the case in the recent report by Newbold *et al.* (1991). Our normal range for values of T/QRS ratio was derived from babies not requiring admission to the neonatal unit. Acidaemia at birth may often represent appropriate fetal adaptation to intrapartum hypoxia (Johnson 1991). If significant birth asphyxia, with subsequent abnormal neurological signs during the early neonatal period, is found to be associated with higher values of T/QRS ratio then ECG analysis may yet have a role in distinguishing physiological from pathophysiological changes in FHR and pH during labour. The objective would be to reduce the frequency of false positive diagnoses of fetal distress, based on CTG alone, and thereby reduce the high rate of operative deliveries associated with continuous electronic FHR monitoring (Thacker 1991). The abnormal range of T/QRS ratio values must be clearly established, not based on acidaemia or CTG criteria, but on follow-up of babies with convincing clinical birth asphyxia. Thus, a much larger clinical experience than is presently available is required before any consideration can be given to the introduction of T/QRS ratio into routine clinical practice.

Acknowledgments

We acknowledge the help of Jessie Heah who collected some of the data, Angela Lee for statistical advice, and the labour ward midwives for their cooperation during this study. We thank Cinventa UK for the loan of the STAN monitor.

References

Arulkumaran S., Lilja H., Lindecrantz K., Ratnam S. S., Thavarasah A. S. & Rosen K. G. (1990) Fetal ECG waveform surveillance should improve fetal surveillance in labour. *J Perinat Med* **18,** 13–22.

Beard R W., Filshie G. M., Knight C. A. & Roberts G. M. (1971) The significance of the changes in the continuous fetal heart rate in the first stage of labour. *J Obstet Gynaecol Br Commonw* **78,** 865–881.

Cohn E. H., Sacks E. J., Heymann M. A. & Rudolph A. M. (1974) Cardiovascular responses to hypoxemia and acidemia in fetal lambs. *Am J Obstet Gynecol* **120,** 817–824.

Dennis J., Johnson A., Mutch L., Yudkin P. & Johnson P. (1989) Acid-base status at birth and neurodevelopmental outcome at four and one half years. *Am J Obstet Gynecol* **161,** 213–220.

Eskes T. K. A. B., Jongsma H. W. & Houx P. C. W. (1983) Percentiles for gas values in human umbilical cord blood. *Europ J Obstet Gynecol Reprod Biol* **14,** 341–346.

Fee S. C., Malee K., Deddish R., Minoque J. P. & Socol M.L. (1990) Severe acidosis and subsequent neurologic status. *Am J Obstet Gynecol* **162.** 802–806.

FIGO News (1987) Guidelines for the use of fetal monitoring. *Int J Gynecol Obstet* **25,** 159–167.

Greene R., Dawes G. S., Lilja H. & Rosen K. G. (1982) Changes in the ST waveform of the fetal lamb electrocardiogram with hypoxia. *Am J Obstet Gynecol* **144,** 950–958.

Gu W., Jones E. T. & Parer J. T (1985) Metabolic and cardiovascular effects on fetal sheep of sustained reduction of uterine blood flow. *J Physiol* **363,** 109–129.

Heinrich J. (1982) Elective fetal monitoring and obstetrical operative frequency. *Europ J Obstet Gynecol Reprod Biol* **14,** 143–152.

Itskovitz J., Goetzman B. W. & Rudolph A. M. (1982) The mechanisms of late decelerations of the heart rate and its relationships to oxygenation in normoxemic and chronically hypoxemic fetal lambs. *Am J Obstet Gynecol* **142,** 66–73.

Jenkins H. M. L., Symonds E. M., Kirk D. L. & Smith P. R. (1986) Can fetal electrocardiography improve the prediction of intrapartum fetal acidosis? *Br J Obstet Gynaecol* **93,** 6–12.

Johnson P. (1991) Fetal distress or physiological adaptation? In *Fetal Monitoring* (Spencer J. A. D., ed.), Oxford University Press, pp. 28–33.

Josten B. E., Johnson R. B. & Nelson J. P. (1987) Umbilical cord blood pH and Apgar scores as an index of neonatal health *Am J Obstet Gynecol* **157,** 843–848.

Kubli F. W., Hon E. H., Khazin A. F. & Takemura H. (1969) Observations on heart rate and pH in the human fetus during labour. *Am J Obstet Gynecol* **104,** 1190–1206.

Lilja H., Greene K.R., Karlsson K. & Rosen K. G. (1985) ST waveform changes of the fetal electrocardiogram during labour—a clinical study. *Br J Obstet Gynaecol* **92,** 611–617

Lilja H., Arulkumaran S., Ratnam S. S. & Rosen K. G. (1988) Fetal ECG during labour: a presentation of a microprocessor system. *J Biomed Eng* **10,** 348–350.

Murphy K. M., Johnson P., Moorcraft J., Pattinson R., Russell V. & Turnbull A (1990) Birth asphyxia and the intrapartum cardiotocograph. *Br J Obstet Gynaecol* **97,** 470–479.

Newbold S., Wheeler T., Clewlow F. & Soul F. (1989) Variation in the T/QRS ratio of fetal electrocardiograms recorded during labour in normal subjects. *Br J Obstet Gynaecol* **96,** 144–150.

Newbold S., Wheeler T. & Clewlow F. (1991) Comparison of the T/QRS ratio of the fetal electrocardiogram and the fetal heart rate during labour and the relation of these variables to condition at delivery. *Br J Obstet Gynaecol* **98,** 173–178.

Parer J. T., Krueger T. R. & Harris J. L. (1980) Fetal oxygen consumption and mechanisms of heart rate response during artificially produced late decelerations of the fetal heart rate in sheep. *Am J Obstet Gynecol* **136,** 478–482.

Rosen K. G., Dagbartsson A., Henrikkson B. A., Lagerkrantz H. & Kjellmer I. (1984) The relationship between circulating catecholamines and ST waveform in the fetal lamb electrocardiogram during hypoxia. *Am J Obstet Gynecol* **149,** 190–195.

Rosen K. G. (1986) Alterations in the fetal electrocardiogram as a sign of fetal asphyxia—experimental data with a clinical implementation. *J Perinat Med* **14,** 355–363.

Rosen K. G. & Lindencrantz K. (1989) STAN—the Gothenburg model for fetal surveillance during labour by ST analysis of the fetal electrocardiogram. *Clin Phys Physiol Meas* **10,** suppl B, 51–56.

Ruth V. J. & Raivio K. O. (1988) Perinatal brain damages: predictive value of metabolic acidosis and Apgar score. *Br Med J* **297,** 24–27.

Siggaard-Andersen O. (1971) An acid base chart for arterial blood with normal and patho-physiological reference areas. *Scand J Clin Lab Invest* **27,** 239–245.

Sykes G. S., Molloy P. M., Johnson P., Gu W., Ashworth F., Sturrat G. M. & Turnbull A. C. (1982) Do Apgar scores indicate asphyxia? *Lancet* **1,** 494–496.

Tejani N., Mann L. I., Bhakthavathsalan A. & Weiss R. R. (1975) Correlation of fetal heart rate—uterine contractions patterns with fetal scalp blood pH. *Obstet Gynecol* **46,** 392–396.

Thacker S. B. (1991) Effectiveness and safety of intrapartum fetal monitoring. In *Fetal Monitoring* (Spencer J. A. D., ed.), Oxford University Press, pp. 211–217.

Wald N. & Cuckle H. (1989) Reporting the assessment of screening and diagnostic tests. *Br J Obstet Gynaecol* **96,** 389–396.

Wheble A M., Gillmer M. D. G., Spencer J. A. D. & Sykes G. S. (1989) Changes in fetal monitoring practice in the UK: 1977–1984. *Br J Obstet Gynaecol* **96,** 1140–1147.

Young D. C., Gray J. H., Luther E. R. & Peddle L. J. (1980) Fetal scalp blood pH sampling: its value in an active obstetric unit. *Am J Obstet Gynecol* **136,** 276–281.

Received 20 December 1990
Resubmitted 22 July 1991
Accepted 18 August 1991

British Journal of Obstetrics and Gynaecology
January 1992, Vol. 99, pp. 32–37

FETAL AND NEONATAL MEDICINE

Clinical assessment of fetal electrocardiogram monitoring in labour

KARL W. MURPHY
VIRGINIA RUSSELL
PAUL JOHNSON

Nuffield Department of Obstetrics and Gynaecology

John Radcliffe Hospital, Maternity Department, Headington,
Oxford OX3 9DU, UK

JANE VALENTE

Department of Gynaecology,
Churchill Hospital, Oxford OX3 7LJ, UK

ABSTRACT

Objective To assess the potential clinical value of fetal electrocardiographic (ECG) monitoring in labour.

Design Descriptive study of the use of ECG waveform analysis during labour and its correlation with other indices of fetal and neonatal well-being.

Setting Teaching hospital in Oxford.

Subjects 86 high risk pregnancies.

Main outcome measures Suitability of ST Segment Analyser (Cinventa, Sweden) for clinical use; relation between the T/QRS ratio during labour (an index of ST segment and T wave elevation) and intrapartum cardiotocography, umbilical artery pH at birth and Apgar scores; T/QRS ratio trends in labour.

Results The system was robust and user-friendly. No statistically significant relation was found between T/QRS ratios in labour and FHR abnormalities in the cardiotocograph. There was a weak relation between T/QRS ratios and umbilical artery acidosis: at a cervical dilatation of 4 cm, the Spearman rank correlation of the mean T/QRS ratio with umbilical artery actual base deficit was $r = -0{\cdot}31$, $0{\cdot}05 > P > 0{\cdot}01$. The correlation of T/QRS with the umbilical artery pH was not statistically significant, although a trend was present (Spearman rank: $r = -0{\cdot}26$, $P > 0{\cdot}05$). Correlation of the T/QRS ratio with Apgar scores at 1 and at 5 min was not statistically significant. Only 3 of 16 infants with an Apgar score of <7 at 1 min had a mean T/QRS ratio above 0·25 at any time during labour.

Conclusions Further research is necessary before a decision can be made whether this new method of fetal monitoring should be introduced into clinical practice.

The deficiencies of electronic FHR (fetal heart rate) monitoring in labour are well recognised (Sykes *et al.* 1983) and there is an urgent need to find better methods of intrapartum fetal surveillance (Sawers 1983). It has been suggested that continuous monitoring of the waveform of the fetal electrocardiogram (ECG) in labour may be a useful method for detecting fetal hypoxia and acidosis (Jenkins *et al.* 1986). Many of the technical problems associated with automated measurements of the fetal ECG waveform have been overcome in recent years. Various systems based on computer averaging have been developed to improve the signal-to-noise ratio. One such system is the ST segment analyser (STAN).

The STAN was constructed in Gothenburg, Sweden, based on evidence from animal studies that the main response to fetal hypoxaemia was a progressive increase in the amplitude of the T wave, together with elevation of the ST segment (Rosen & Kjellmer 1975). Work by Hokegard *et al.* (1979) and Greene *et al.* (1982) showed that ST waveform elevation occurred when fetal hypoxia led to anaerobic myocardial metabolism. Changes in the ST segment and T wave are known to appear in advance of cardiovascular failure (Rosen *et al.* 1976). Essentially, the STAN produces a continuous read-out of the ratio between the amplitude of the T wave and the amplitude of the QRS complex (T/QRS ratio), together with intermittent plots of the computer-averaged fetal ECG waveform, throughout labour.

The aim of this descriptive study was to investigate the potential of ST waveform monitoring in labour as a clinical tool. ST waveform changes were correlated with changes in the intrapartum cardiotocogram (CTG) and with indices of the infant's condition at birth: Apgar scores and umbilical cord acid-base measurements.

Subjects and methods

Fetal ECG recordings were obtained from 86 women who had continuous electronic fetal heart rate monitoring during labour. In this hospital 50% of all women required intrapartum electronic monitoring during the study period and it was from this group that subjects were recruited into the study. Availability of the equipment and research staff determined whether any woman from this group would be asked to participate. The major indications for fetal monitoring in the study group were as follows: (1) antepartum: hypertension/intrauterine growth retardation 28%, prolonged pregnancy 13%, previous cae-

---

Correspondence: Dr Karl Murphy, Senior Registrar & Fellow in Fetal Medicine, Department of Obstetrics and Gynaecology, The Queen Mother's Hospital, Yorkhill, Glasgow G3 8SH, UK.

sarean section 6%, miscellaneous 9%; (2) intrapartum: in 24% monitoring was started during labour because oxytocin or epidural analgesia were used. Meconium staining of the amniotic fluid was the indication for monitoring in a further 16%. Fetal distress diagnosed by auscultation was the indication in 4%.

Table 1 shows the obstetric characteristics of the study population. Fifty eight (67%) were nulliparous. The mean age was 26 (range 18–34). There was a high frequency of induction of labour, epidural anaesthesia and instrumental and operative deliveries. Fetal outcome was assessed by Apgar scores, cord blood acid-base measurements at delivery (using Radiometer ABL3 blood gas analyser) and the need for admission to the neonatal special care unit. Apgar scores were recorded for all the babies. The pH, Po_2, Pco_2 and base deficit were determined in blood from the umbilical artery and the vein for 97% of the babies. The 'actual' base deficit was estimated: this is a measure of the metabolic component of the acidosis that is not corrected for Pco_2 level. The base deficit in the extracellular fluid was also calculated using the Siggaard-Andersen acid-base chart (1971) and this is more representative of the true metabolic component of the acidosis. Umbilical artery acidosis, pH<7·12 (1 SD below the mean, Sykes *et al.* 1983) and low Apgar scores (<7 at 1 min) were relatively frequent because the study group contained many high-risk pregnancies.

The STAN prototype has been described in detail elsewhere (Lilja *et al.* 1988) and only the main features will be presented here. The fetal ECG signal is obtained from a standard, single spiral scalp electrode. A unipolar scalp lead with the maternal thigh as reference (second electrode) makes it possible to identify the T wave and, at the same time to decrease signal noise. The vector ECG aspects of T wave recording have been clarified by Lindecrantz *et al.* (1988). Both electrodes are connected to a patient isolation box, size 132×67×35 mm, via an ECG clip connector. The ECG signal is amplified in the patient isolation box. The main unit, where most of the signal processing and the computations are performed, is housed in a box measuring 385×415×107 mm. The main unit is furnished with a printer for data presentation, a graphic liquid crystal display and five push-buttons with software controlled functions.

Table 1. Obstetric characteristics of the study population (*n*=86)

Population characteristics (*n*=86)	*n*	(%)
Primigravidae	58	(67)
Gestation >42 weeks	12	(14)
Gestation <37 weeks	5	(6)
Induction of labour	51	(59)
Prostaglandin	42	(49)
Oxytocin	51	(59)
Pethidine	30	(35)
Epidural anaesthesia	57	(66)
Meconium	25	(29)
Operative delivery—fetal distress	24	(28)
Caesarean section	9	(10)
Breech	2	(2)
Cord entanglement	16	(19)
Birthweight <10th centile	4	(5)
Umbilical artery pH <7·12	11	(13)
Apgar score <7 at 1 min	18	(21)
Admission to special care unit (for asphyxia)	1	(1)

In the main unit, the fetal ECG signal from the patient isolation box is passed initially through an adaptive line-frequency filter. This is then split into two paths, one which is low-pass-filtered at 100 Hz and the other is band-pass-filtered at 5 to 60 Hz. Both ECG signals are fed through software-controlled adjustable gain amplifiers. The ECG signal is then A/D converted at a rate of 500 Hz, with a resolution corresponding to eight bits. A software QRS detector works on the band-pass-filtered ECG signal and detects fetal ECG complexes. Averaging is performed on the low pass filtered fetal ECG. The height of the T wave is measured in the averaged complex. The T wave elevation is quantified as the ratio between the QRS peak-to-peak amplitude and the T wave elevation above the level of the P–Q interval.

The processed data are shown on both the liquid crystal display and the printer. The T/QRS ratios are presented as a function of time and, every minute, an averaged fetal ECG complex is plotted on the printer.

For each labour in the study the mean T/QRS ratio was calculated from one-hour recordings at cervical dilatations of 4 cm, 8 cm, and 10 cm. An hour of recording provided a mean of 20 (SD 10·4) T/QRS ratios. When the exact cervical dilatation was unknown a linear rate of change over time was assumed. When calculating the mean T/QRS ratios at 4 cm, 8 cm and 10 cm, the hour of recording immediately after the time of the known or assumed cervical dilatation was used. Therefore, mean T/QRS values were obtained on three separate occasions from women who were monitored throughout the whole of their labours, whereas data were obtained on only two or even one occasion when monitoring was begun during labour. For the purpose of this analysis T/QRS ratios above 0·25 in the first or second stage of labour were considered to be outside the normal range (Lilja *et al.* 1988). The intrapartum CTG was classified as normal according to the criteria set out by Steer *et al.* (1989).

The χ^2 test with Yates' correction and Fisher's exact test were used to compare proportions in the analysis of the CTG. The Spearman rank correlation coefficient and the Mann-Whitney *U* test were used to analyse the relation between mean T/QRS ratios and both the Apgar scores and umbilical cord blood variables at delivery. Friedman two-way analysis of variance by ranks was used to study the stability of the T/QRS ratios throughout labour. Results were considered significant at the $P<0{\cdot}05$ level.

Results

The STAN system was found to be robust and suitable for clinical application. Eighty-six fetal ECG recordings were obtained, of which three were completely unsuitable for analysis because the signal quality was consistently poor. The overall number of fetal ECG waveforms obtained (each one being an average of 10 actual ECG complexes) was 10 667 of which 6982 were suitable for analysis (65%). The major cause of poor signal quality was 50 Hz interference. The mean duration of the recordings from the first stage of labour was 181 (SD 135) min, median 160 min, interquartile range 80–260 min. The mean duration of the second stage labour recordings was 81 (SD 50) min, median 70 min, interquartile range 40–105 min. The mean cervical dilatation at application of the ST segment

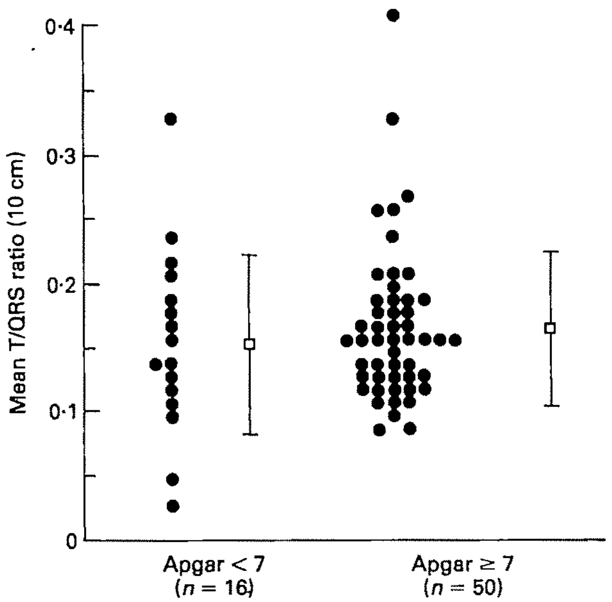


Fig. 1. Relation between STAN (one-hour mean T/QRS ratio at a cervical dilatation of 10 cm) and Apgar score at 1 min. The mean T/QRS ratio of infants with a 1-min Apgar score <7 was 0·15 (SD=0·07, n=16) compared with 0·16 (SD 0·06, n=50) for those with a score >6; Mann-Whitney test, U=373, P=0·68).

analyser (STAN) was 5·7 (SD 2·6) cm. Data were available for the calculation of one-hour mean T/QRS ratios from 44 women at 4 cm cervical dilatation, from 60 women at 8 cm dilatation and from 68 in the second stage of labour (10 cm). Mean T/QRS ratios at all three stages (4 cm, 8 cm & 10 cm) were available for 32 women, two mean ratios were available for 25 and one mean ratio was available for the remaining 26.

The one-hour mean T/QRS values at 4 cm, 8 cm and 10 cm were analysed longitudinally to look for a change in the ratio with the progression of the labour. The Friedman two-way analysis of variance by ranks was used in the 32 labours for which all three one-hour mean T/QRS ratios were available. The median ratio was 0·178 at 4 cm, 0·175 at 8 cm and 0·160 at 10 cm; the grand median was 0·171. The difference was not statistically significant (S=3·7, df=2, P=0·16, n=32), indicating that the T/QRS ratio was relatively stable throughout labour.

At 4 cm of cervical dilatation 4 of 17 women with an abnormal CTG in the first stage of labour had a mean T/QRS ratio above 0·25 compared with 2 of 27 with a normal CTG (Fisher's exact test: difference not statistically significant). The results were very similar at 8 cm and 10 cm.

No significant relation between T/QRS ratios and Apgar scores was found: only 3 of 16 infants with an Apgar score <7 at 1 min had a mean one-hour T/QRS ratio above 0·25 at any of the three stages of cervical dilatation studied. Similarly, only one of five infants with a 1-min Apgar score <4 had a mean one-hour T/QRS ratio above 0·25. The mean one-hour T/QRS ratio at 10 cm was 0·15 (SD 0·07) for those with a 1-min Apgar score <7 (n=16) and 0·16 (SD 0·06) for those with a 1-min Apgar score >6 (n=50) (Mann-Whitney test, U=373, P=0·68, Fig. 1). The correlation of the mean one-hour T/QRS ratio at 10 cm with the 1-min Apgar score was not statistically significant (Spearman rank correlation coefficient r=0·07, n=44, P>0·05). Results were similar for the correlations between T/QRS ratios at 8 cm and 10 cm dilatation and Apgar scores at 1 and at 5 min. In this study only one infant had a 5-min Apgar score <7 and this followed a caesarean section for dystocia, under general anaesthesia. The cord pH and gases were normal and birth asphyxia was probably not the reason for this infant's depression. The mean T/QRS ratio was normal.

Cord blood acidosis

The correlation of the one-hour mean T/QRS ratios at 4 cm dilatation with umbilical artery actual base deficit was statistically significant: Spearman rank correlation coefficient r=0·31, n=39, P<0·05. The correlation with the umbilical artery pH was not statistically significant but a trend was present (Spearman rank correlation coefficient r=0·26, n=39, 0·05<P<0·10). Also, the group with an umbilical artery pH <7·12 had a higher mean T/QRS ratio at 4 cm dilatation (mean 0·25 SD 0·10, n=7) than the group with a pH ≥7.12 (mean 0·18 SD 0·16, n=32) but again this trend did not reach statistical significance (Mann-Whitney test, U=373, P=0·68, Fig. 2).

Eleven infants had an umbilical artery pH<7·12 (1 SD below mean: Sykes *et al.* 1983). The mean one-hour T/QRS ratio at any of the three stages of cervical dilatation studied was above 0·25 in 4 of these 11 compared with 7 of 69 without acidosis (χ^2 with Yates' correction = 3·5, 1 df, 0·05<P<0·10). There was no significant correlation between the mean one-hour T/QRS ratios at 8 cm and 10 cm and umbilical artery pH or base deficit measurements. Neither was there any significant correlation between umbilical artery $P\text{o}_2$, $P\text{co}_2$ nor the umbilical vein pH or blood gas measurements and the mean T/QRS ratios.

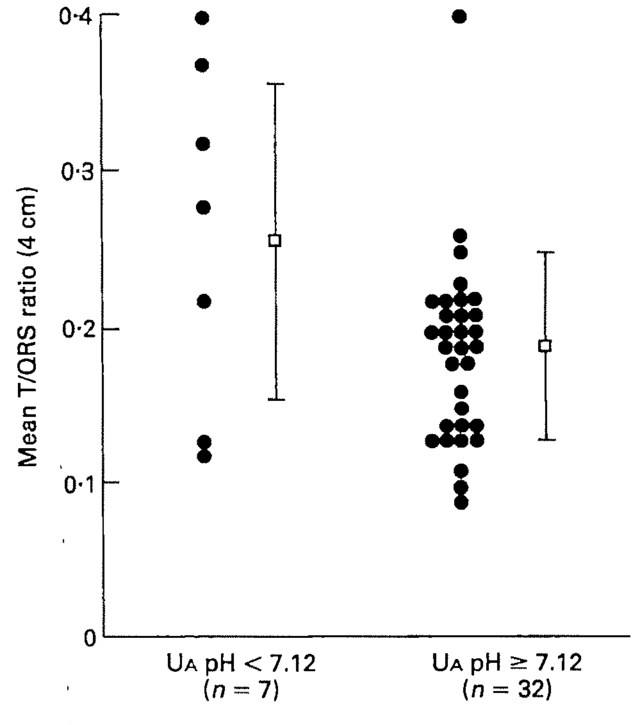


Fig. 2. Relation between the 1 hour mean T/QRS ratio at a cervical dilatation of 4 cm and the umbilical artery (Ua) pH at birth. The mean T/QRS ratio was higher in infants with a pH <7·12 (mean 0·25, SD 0·10, n=7) than in those with a pH ≥7·12 (mean 0 18, SD 0·06, n=32) but the difference was not statistically significant (Mann-Whitney test, U=187, P=0·09).

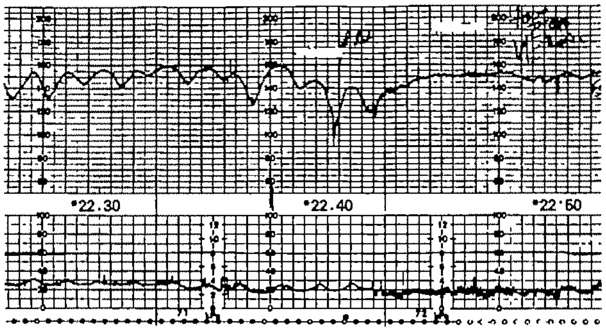


Fig. 3. Cardiotocograph in patient no. 4 (Table 2) showing the fetal heart rate pattern during the period before delivery. This ominous recording showed late decelerations of the fetal heart rate in association with absent baseline variability. The T/QRS ratios were abnormal during labour and the infant was born in poor condition.

Metabolic acidosis

Of the 11 infants who had cord blood acidosis (as defined above) seven had a mainly respiratory acidosis and four a clinically significant metabolic acidosis (umbilical artery pH$<$7·12 plus extracellular-fluid base-deficit $>$12 mM/l). A mean one-hour T/QRS ratio above 0·25 in the first or second stage of labour identified only one of the four infants with a true metabolic acidosis at birth. Their data are shown in Table 2. An abnormal CTG identified three of these four infants.

Number 1 was a breech delivery and the FHR changes that were observed during the last hour of labour were probably caused by umbilical cord compression. The STAN was disconnected from the fetus 30 min before delivery to facilitate transfer to the operating theatre, and it was during this time that the FHR changes were most severe. Therefore, this fetus was really only significantly hypoxic after the STAN monitoring was discontinued and this result cannot be regarded as a false negative. Fetal ECG waveforms were inverted throughout labour in those presenting by the breech.

In patient 2, the FHR changes lasted for 70 min and were also suggestive of umbilical cord compression. At birth the cord was wrapped tightly around the infant's neck. Although T/QRS ratios were not raised above 0·25 during labour, the ratio did show an increase from 0·11 (mean one-hour T/QRS ratio at a cervical dilatation of 4 cm) to values ranging between 0·20 and 0·25 before birth.

Cord blood metabolic acidosis was an isolated finding in patient no. 3, the infant had a normal CTG through labour and no signs of depression at delivery. The T/QRS ratios also remained normal throughout labour.

Patient no. 4 had the most severely asphyxiated infant in this study. Labour was induced at 42 weeks gestation because of mild hypertension without proteinuria. Two hours after the membranes were ruptured meconium stained amniotic fluid was observed. The FHR was unreactive and showed some reduction in baseline variability. During the last 90 min of labour the FHR pattern became particularly ominous, demonstrating absent baseline variability and repeated late decelerations (Fig. 3). The infant was born by forceps in poor condition with an umbilical artery pH of 6·96 and a 1-min Apgar score of 2; the birthweight was 3789 g. The infant was ventilated through an endotracheal tube for 5 min and had an apparently good response to resuscitation, but by one hour of age the infant was grunting, and repeat capillary blood gas measurements showed that the pH had remained at 6·97 and the $P\text{co}_2$ had increased from 63 mmHg at delivery to 82 mmHg. Despite this, the extracellular fluid base deficit had decreased from 16 to 12·5 mM/l indicating some improvement in the metabolic component of the acidosis. At this stage the infant was transferred to the special care unit and oxygen was administered via a head-box. By two hours of age capillary blood gas measurements were within normal limits. No seizures occurred in the neonatal period, and neurological examinations, both at the time of discharge from the special care unit and at 6 months of age, were normal.

In patient no. 4, during the first stage of labour the fetal ECG waveforms demonstrated clear ST elevation in association with an increase in T wave amplitude (Fig. 4). These changes were present early in labour, the one-hour mean T/QRS ratios were 0·36 and 0·30 at 4 cm and 8 cm, respectively. Towards the end of the second stage of labour the ST segment demonstrated a biphasic pattern with negative T waves and ST depression and the T/QRS ratio actually decreased: the one-hour mean ratio at 10 cm was only 0·21 (Fig. 5).

Other markers of fetal distress were studied (Table 1). Umbilical cord entanglement was observed in 16 infants of whom only one had high mean T/QRS ratios in labour and this infant was normal. Of these 16 infants 10 had an abnormal CTG, seven had a 1-min Apgar score of $<$7 and two had a metabolic acidosis in cord artery blood. None had high T/QRS ratios in labour.

Meconium stained amniotic fluid was present in 25 labours. Five of these had one-hour mean T/QRS ratios above 0·25 compared with 6 out of 57 without meconium (χ^2 with Yates' correction = 0·54, 1 df, $P>0{\cdot}05$).

Table 2. Details of four labours associated with umbilical artery blood metabolic acidosis at delivery*

Patient No	Duration of abnormal CTG (min)	Mode of delivery	Apgar score		Umbilical artery			1 h mean T/QRS†
			1 min	5 min	pH	$P\text{co}_2$ (mmHg)	BDecf (mmol/l)	
1	60	Breech	3	7	6·97	82	12·5	<0·25
2	70	Normal	4	8	6·89	92	14·0	<0·25
3	0	Forceps	9	10	7·11	43	14·0	<0·25
4	90	Forceps	2	7	6·96	63	16·0	>0·25

*Metabolic acidosis was defined as a pH <7·12 plus an extracellular fluid base deficit (BDecf) of >12·0 mmol/l. Patients 1 and 2 also had a marked respiratory acidosis and patient no. 4 had an abnormal T/QRS ratio and gave birth to the most severely affected infant.

†At 4, 8 or 10 cm cervical dilatation.

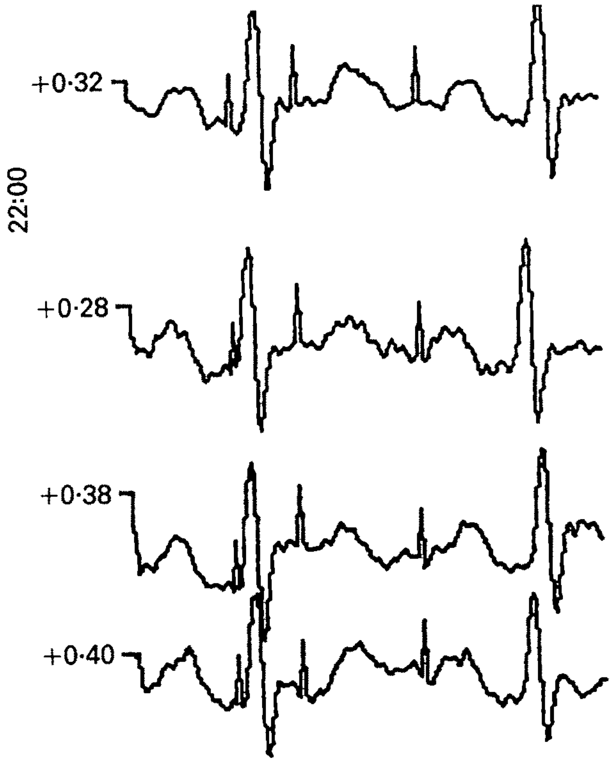


Fig. 4. Fetal electrocardiographic (ECG) waveforms from the first stage of labour in patient no. 4. The waveforms showed ST elevation and high amplitude T waves. The T/QRS ratios are shown on the left of the waveforms and were consistently above 0·25.

The difference between the one-hour mean T/QRS ratio at 4 cm and that at 10 cm was measured for each of the acidotic infants (data available for six labours) and the non-acidotic infants (data available for 27 labours) and the results were compared: there was no evidence of an increment in the T/QRS ratio in the acidotic infants compared with the non-acidotic infants-Mann-Whitney test, U=57, Z=1·24, P=0·26.

Discussion

This study has shown no clear relation between ST waveform changes, as measured by the T/QRS ratio, and both the intrapartum CTG and indices of the infant's condition at birth. The study lacks power because of the small numbers of seriously distressed fetuses but it is obvious that the relation between the T/QRS ratio and the traditional markers of fetal and neonatal well-being is complex and may not be clinically useful.

A clearly defined end-point is necessary for the assessment of a new method of intrapartum fetal surveillance. This poses two problems for the obstetrician. First, there is no universally accepted definition of birth asphyxia. Second, the occurrence of severe birth asphyxia is relatively rare. In the study by Lilja *et al.* (1988) of T/QRS ratios in labour there were no acidotic fetuses (23 cord pH measurements) though half the pregnancies were described as high risk. In our study, in which all the pregnancies were high risk, there were 11 acidotic infants, four of whom had a significant metabolic acidosis. These numbers are still small and a much larger study would be required if perinatal mortality or long term neurological injury were chosen as end-points, because of their rarity.

We found no relation between T/QRS ratios and the intrapartum CTG. Other workers have shown an association between changes in the ST waveform and the intrapartum CTG (Pardi *et al.* 1974; Lilja *et al.* 1985) and, although ST waveform changes occur independently of FHR change, a relation would be expected if both were related to hypoxia.

The STAN was not a good predictor of clinical depression at birth (1-min Apgar scores <7 or <4) although it did identify the one infant in whom the depression was almost certainly due to in-utero hypoxia (no. 4 Table 2). Two of the other three infants with true metabolic acidosis were also depressed at birth (nos. 1 and 2 Table 2). In patient no. 1 the hypoxic insult occurred after STAN monitoring was discontinued and in no. 2 the T/QRS ratio did increase before delivery, albeit to less than 0·25. With regard to the other infants with a low Apgar score at birth other causes of clinical depression must be borne in mind such as sedative drugs or anaesthesia in labour, airway obstruction, infection, trauma and immaturity (Bowe *et al.* 1970).

There was a weak but statistically significant correlation between the T/QRS ratio at 4 cm dilatation and the umbilical artery actual base deficit (r=0·31, P<0·05). It is difficult to know how to interpret this because the correlations were not significant when the one-hour mean T/QRS ratios at 8 cm and 10 cm were analysed and the numbers were greater in these groups. Furthermore, only one of the four infants with a true metabolic acidosis, as defined by a pH <7·12 plus an extracellular base deficit of >12 mM/l, had raised T/QRS ratios during

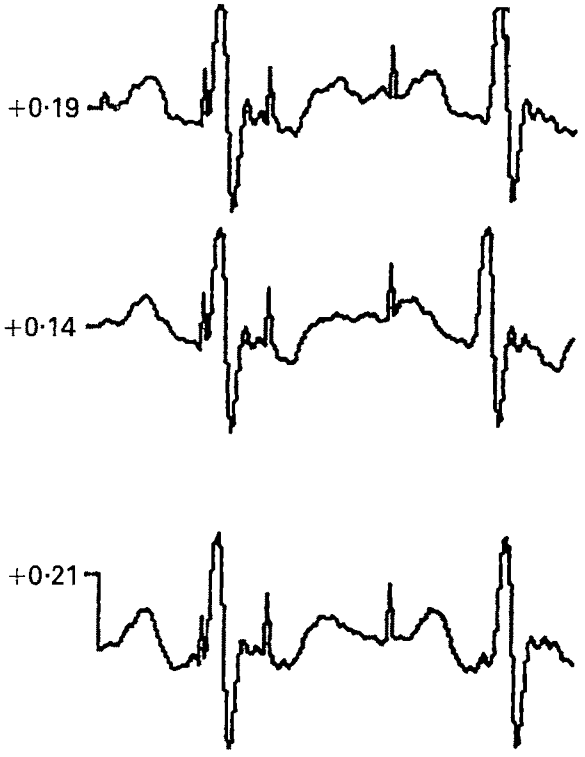


Fig. 5. Fetal electrocardiographic waveforms from the second stage of labour in patient no. 4. Although the actual T/QRS ratios (shown on the left of the waveforms) were normal (<0·25) the ST segment showed an unusual biphasic pattern with ST depression and T wave inversion. This pattern evolved from one of ST and T wave elevation during the first stage of labour (see Fig. 4).

labour and it is in this group that ST waveform changes would be most expected. Based on earlier animal studies, it has been proposed that hypoxia and anaerobic metabolism lead to myocardial glycogenolysis which releases potassium ions which in turn cause elevation of the T wave of the fetal ECG (Rosen & Isaksson 1976).

Similarly negative findings regarding the relation between T/QRS ratios and metabolic acidosis have been reported recently by Newbold *et al.* (1991). The absence of a correlation of ST elevation with the fetal pH has been shown by Pardi *et al.* (1974) and Lilja *et al.* (1985) although the latter did show a correlation with umbilical cord lactate levels, possibly a more sensitive index of cellular hypoxia. Even this needs further validation as the numbers were small.

It was found that the T/QRS ratio was a relatively stable measurement throughout labour, with little change occurring in the values for an individual fetus. No statistically significant difference was found between the 4 cm and the 10 cm one-hour mean T/QRS ratios in either the acidotic or the non-acidotic infants. Moreover, the fact that an abnormal T/QRS ratio reverted to a normal value during the second stage of labour in patient no. 4 (Table 2), in spite of a high ratio in the first stage of labour and an obvious biphasic ST waveform with ST depression in the second stage, indicates the potential danger of relying on the analysis of a single component of the fetal ECG waveform.

The potential role of STAN in intrapartum fetal monitoring might be an improvement in the specificity for the detection of birth asphyxia as poor specificity is one of the major shortcomings of CTG monitoring in labour (Murphy *et al.* 1990). Obviously, this would have to be accompanied by a high sensitivity for the detection of asphyxia and the numbers in this study are too small to allow realistic comment on the sensitivity of STAN. It is encouraging that the most severely asphyxiated infant was identified by an abnormal ECG waveform but worrying that most infants with moderate acidosis and depression were not identified. If fetal ECG monitoring has a role in labour in the future it might be in conjunction with the CTG if it can be shown to reduce the need for intervention, both fetal blood sampling and operative delivery, that results from the high false positive rate associated with CTG monitoring. Further data are needed and a large multicentre European Community trial is currently in progress. It is important that this new method of intrapartum fetal monitoring is not introduced prematurely into clinical practice.

Acknowledgments

We are grateful to Dr K. G. Rosen (Gothenburg, Sweden) for providing us with the STAN monitor and for his helpful comments and suggestions about the manuscript and to Dr Gordon Murray (Western Infirmary, Glasgow) for statistical advice.

References

Bowe E. T., Beard R. W, Finster M., Poppers P. J., Adamsons K. & James L. S. (1970) Reliability of fetal blood sampling. *Am J Obstet Gynecol* **107**, 279-287.

Greene K. R., Dawes G. S., Lilja H. & Rosen K. G. (1982) Changes in the ST waveform of the fetal lamb electrocardiogram with hypoxaemia. *Am J Obstet Gynecol* **144**, 950-958.

Hokegard K. H., Karlsson K , Kjellmer I. & Rosen K. G. (1979) ECG changes in the fetal lamb during asphyxia in relation to beta-adrenoceptor stimulation and blockade. *Acta Physiol Scand* **105**, 195-203.

Jenkins H. M. L., Symonds E. M., Kirk D. L. & Smith P. R. (1986) Can fetal electrocardiography improve the prediction of intrapartum fetal acidosis? *Br J Obstet Gynaecol* **93**, 6-12.

Lilja H., Greene K. R., Karlsson K. & Rosen K. G. (1985) ST waveform changes of the fetal electrocardiogram during labour—a clinical study. *Br J Obstet Gynaecol* **92**, 611-617.

Lilja H , Arulkumaran S., Ratnam S. S. & Rosen K. G. (1988) Fetal ECG during labour: a presentation of the microprocessor system. *J Biomed Eng* **10**, 348-350.

Lindecrantz K., Lilja H., Widmark C. & Rosen K. G. (1988) Fetal ECG during labour: a suggested standard. *J Biomed Eng* **10**, 351-353.

Murphy K. W, Johnson P., Moorcraft J , Pattinson R., Russell V. & Turnbull A. C. (1990) Birth asphyxia and the intrapartum cardiotocograph. *Br J Obstet Gynaecol* **97**, 470-479.

Newbold S., Wheeler T. & Clewlow F. (1991) Comparison of the T/QRS ratio of the fetal electrocardiogram and the fetal heart rate during labour and the relation of these variables to condition at delivery. *Br J Obstet Gynaecol* **98**, 173-178.

Pardi G , Tucci E., Uderzo A. & Zanini D. (1974) Fetal electrocardiogram changes in relation to fetal heart rate patterns during labour. *Am J Obstet Gynecol* **118**, 243-250.

Rosen K. G., Hokegard K. H. & Kjellmer I. (1976) A study of the relationship between the electrocardiogram and haemodynamics in the fetal lamb during asphyxia. *Acta Physiol Scand* **98**, 275-284.

Rosen K. G. & Isaksson O. (1976) Alterations in fetal heart rate and ECG correlated to glycogen, creatinine phosphate and ATP levels during graded hypoxia. *Biol Neonate* **30**, 17-24.

Rosen K. G. & Kjellmer I. (1975) Changes in the fetal heart rate and ECG during hypoxia. *Acta Physiol Scand* **93**, 59-66.

Sawers R. S. (1983) Fetal monitoring during labour. *Br Med J* **287**, 1649-1650.

Siggaard-Andersen O. (1971) An acid-base chart for arterial blood with normal and pathophysiological reference areas. *Scand J Clin Lab Invest* **27**, 239-245.

Sykes G. S., Molloy P. M., Johnson P., Stirrat G. M. & Turnbull A. C (1983) Fetal distress and the condition of newborn infants. *Br Med J* **287**, 943-945.

Steer P. J., Eigbe F., Lissauer T. J. & Beard R. M. (1989) Interrelationships among abnormal cardiotocograms in labour, meconium staining of the amniotic fluid, arterial cord blood pH and Apgar scores. *Obstet Gynecol* **74**, 715-721.

Received 7 November 1989
Resubmitted 8 April 1991
Accepted 7 October 1991

British Journal of Obstetrics and Gynaecology
January 1992, Vol. 99, pp. 38–42

FETAL AND NEONATAL MEDICINE

Transvaginal sonography for fetal measurement in early pregnancy

ALESSANDRA KUSTERMANN
Il Clinica Ostetrico-Ginecologica, Universita' di Milano, Via Commenda 12, Milano, Italy

ALESSANDRO ZORZOLI
Ospedale San Giuseppe, Via San Vittore 12, Milano, Italy

DANIELE SPAGNOLO
IV Clinica Ostetrico-Ginecologica, Universita' di Milano, Ospedale San Raffaele, Via Olgettina, Milano, Italy

UMBERTO NICOLINI
Royal Postgraduate Medical School, Queen Charlotte's and Chelsea Hospital, Goldhawk Road, London W6 0XG, UK

ABSTRACT

Objective To establish reference ranges for fetal size by gestation in the first trimester as indicated by cephalic, abdominal and limb measurements using transvaginal sonography.
Design A prospective descriptive study.
Setting Two antenatal clinics in Milan, Italy.
Subjects 270 women with normal singleton pregnancies at 42–108 days gestation. All had regular cycles and certain dates.
Interventions Vaginal ultrasound examination including inspection of fetal structures and lasting 5–15 min.
Main outcome measures As many of the following fetal measurements as possible according to gestational age and ease: crown-rump length (CRL), biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), femur and foot lengths.
Results CRL was measured in 183 fetuses, BPD in 201, HC in 162, AC in 160, femur length in 133 and foot length in 62. The best description of the relation of CRL to gestational age was achieved by a quadratic function ($y = -3{\cdot}98 - 0{\cdot}308x + 0{\cdot}0117x^2$). Mean values thus derived were virtually identical to those obtained by Robinson & Fleming in 1975 with transabdominal static scanning. Fetal BPD, HC, AC and femur length correlated more closely with CRL than gestational age. Reference ranges (mean and 95% data intervals) were constructed for each biometrical measurement in relation to gestational age and CRL. The HC/AC and femur/foot length ratios did not show any significant variation with gestational age or CRL.
Conclusions These data may be useful in the early detection of genetic disorders affecting the growth of fetal head, trunk and limbs. Genetic and/or environmental variables play an appreciable role in the modulation of early fetal growth.

Since* the introduction of ultrasound into obstetric practice, fetal growth has been extensively studied in the second and third trimesters of pregnancy. By contrast, few data are available on embryonic growth before 12–13 weeks. The classical studies described by Robinson (1973) and Robinson & Fleming (1975) on crown-rump length (CRL) are still the main reference for assessment of gestational age in the first trimester. Although studies in early pregnancy have since described associations between gestational age and other fetal measurements, such as biparietal diameter (BPD) (Bovicelli *et al.* 1981), cranial apex to ear diameter and abdominal perimeter (Green & Hobbins 1988), the reference ranges so derived have not achieved wide acceptance in practice.

Transvaginal sonography allows the use of higher frequency transducers than with traditional abdominal ultrasound, thus providing superior resolution with earlier and more accurate identification of fetal structures. In view of these advantages, transvaginal sonography is now used in obstetrics for an increasing number of indications (Goldstein 1990). Normal ultrasonic appearance of fetal structures has been described in early gestation (Timor-Tritsch *et al.* 1989) and first trimester diagnosis of fetal malformations has recently been reported (Rottem *et al.* 1989).

Since precise determination of both gestational age and fetal size is a prerequisite for diagnosis of deviations from normality, reference ranges for fetal biometrical measurements in the first trimester are clearly required. However, ranges derived from transabdominal ultrasound using outmoded equipment might not be adequate for measurements obtained with the new transvaginal technique.

The aim of this study was to investigate fetal size in the first trimester as indicated by cephalic, abdominal and limb measurements, and thereby establish reference ranges for use with transvaginal sonography.

Subjects and methods

A total of 270 women attending the antenatal clinics of two

---

*Correspondence: Umberto Nicolini, Il Clinica Ostetrico-Ginecologica, Universita' di Milano, Via Commenda 12, 20122 Milano, Italy.

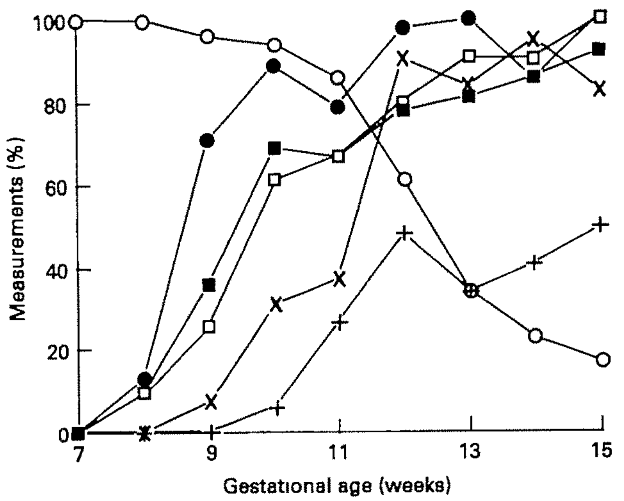


Fig. 1. Percentage of measurements obtained of crown-rump length (CRL), biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), femur and foot length in relation to the total number of fetuses examined per week of gestation. —○—, CRL; —●—, BPD; —■—, HC; —□— AC; —x— femur; —+— foot.

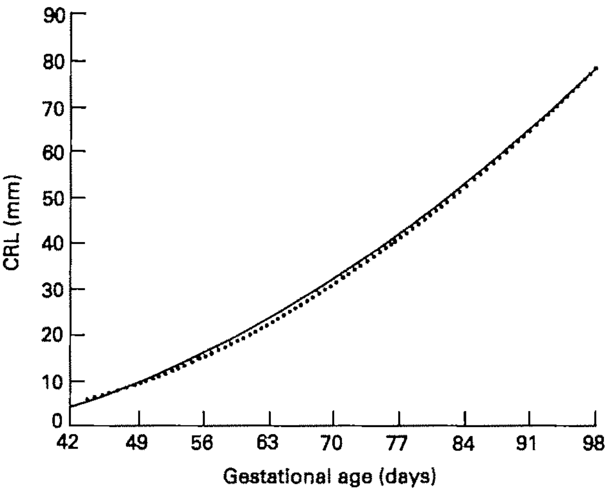


Fig. 2. Mean values of fetal crown-rump length (CRL) obtained in this study and mean values reported by Robinson & Fleming (1975) plotted against gestational age. —— Present series: $y = -3{\cdot}98 - 0{\cdot}308x + 0{\cdot}0117x^2$; .... Robinson's series: $y = 7{\cdot}30 - 0{\cdot}644x + 0{\cdot}0144x^2$.

institutions (Clinica Ostetrico-Ginecologica 'L.Mangiagalli' and Ospedale San Raffaele in Milano, Italy) underwent transvaginal sonography at 42–108 days menstrual age. All had regular cycles (24–32 days), were certain of the first day of the last menstrual period and were not on oral contraception in the three months before conception. None had any known maternal pathology or first trimester bleeding. Four twin pregnancies were excluded.

All women gave informed consent to participate in the study and were examined using commercially available ultrasound equipments. The vaginal probe, either 5 or 6·5 MHz, was coupled with gel and covered with a sterile glove before being introduced into the vagina with the woman lying supine on a colposcopy table. The examination, performed by three of the authors (A.K., A.Z., D.S.), included inspection of fetal structures and lasted from 5–15 min. Three fetuses (1%) diagnosed as having structural malformations (two cystic hygromas and one anencephaly) were excluded from subsequent analysis.

An attempt was made to obtain as many of the following fetal measurements as possible, according to gestational age and ease: CRL, BPD, head circumference (HC), abdominal circumference (AC), femur length and foot length.

We waited for the maximal extention of the fetus in order to measure CRL. Before the appearance of the midline structure, BPD was measured as the largest transverse diameter of the fetal cephalic pole and, thereafter, according to the method of Campbell & Newman (1971). HC was calculated from BPD and the antero-posterior diameter of the head perpendicular to the former, using the formula for an ellipse. AC was measured at the level of fetal umbilical cord insertion when the fetal

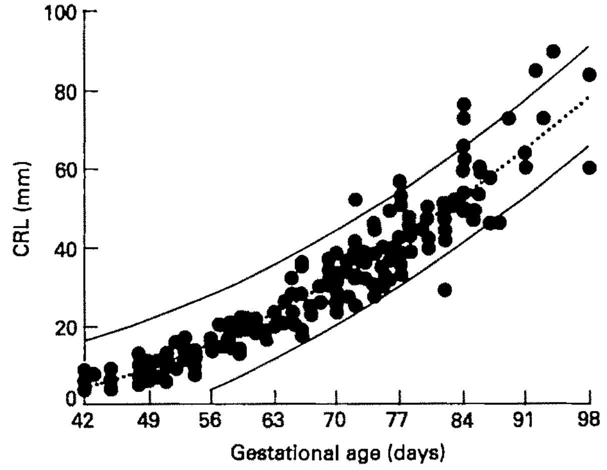


Fig. 3. Individual measurements of fetal crown-rump length (CRL) and reference ranges (mean and 95% data intervals) plotted against gestational age. $y = -3{\cdot}98 - 0{\cdot}308x + 0{\cdot}0117x^2$; SD = 6·08; $r = 0{\cdot}936$.

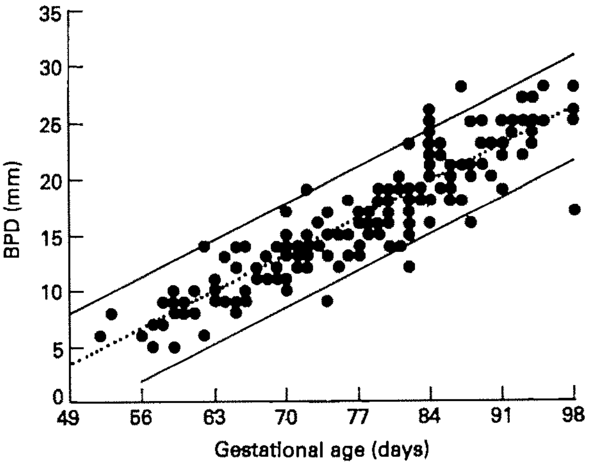


Fig. 4. Individual measurements of fetal biparietal diameter (BPD) and reference ranges (mean and 95% data intervals) plotted against gestational age. $y = -19{\cdot}747 + 0{\cdot}46728x^2$; SD = 2·37; $r = 0{\cdot}930$.

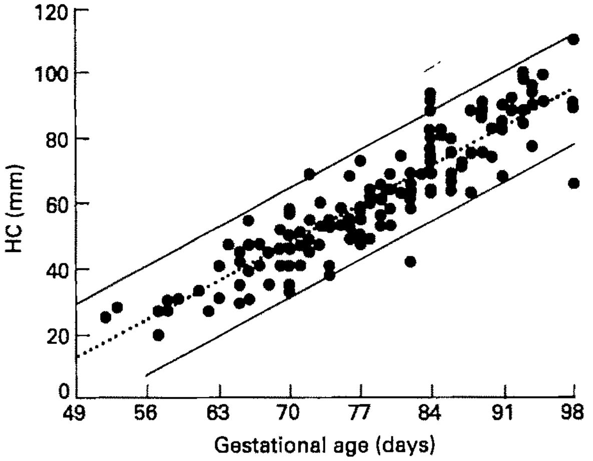


Fig. 5. Individual measurements of fetal head circumference (HC) and reference ranges (mean and 95% data intervals) plotted against gestational age. $y = -71{\cdot}432 + 1{\cdot}6934x^2$; SD = 8·48; $r = 0{\cdot}930$.

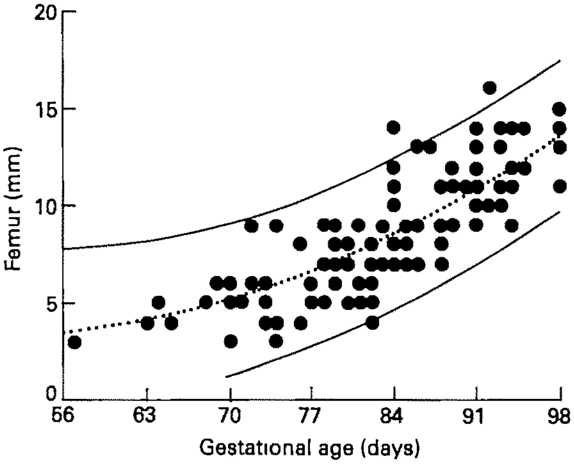


Fig. 7. Individual measurements of fetal femur length and reference ranges (mean and 95% data intervals) plotted against gestational age. $y = 13{\cdot}3 - 0{\cdot}417x + 0{\cdot}00427x^2$; SD = 1·95; $r = 0{\cdot}865$.

stomach and the intrahepatic vein were not identified. Femur and foot lengths were determined on the longest sections obtained. When serial scans were performed in the same woman, only the first measurements obtained were considered for analysis.

The relation of each ultrasonic measurement to gestational age was assessed by least squares regression analysis. Multiple regression analysis was used to assess the relative influence of gestational age and CRL on the changes in BPD, HC, AC and femur length.

Reference ranges were constructed for each measurement in relation to gestational age and CRL values: the Shapiro-Francia 'W' test was used to test the normality of distribution and determine the best transformation required; after exclusion of heteroscedasticity, 95% data intervals (±1·96 SD) were calculated (Royston 1991).

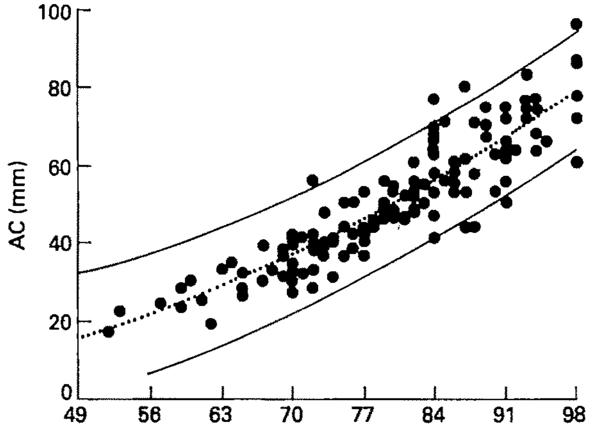


Fig. 6. Individual measurements of fetal abdominal circumference (AC) and reference ranges (mean and 95% data intervals) plotted against gestational age. $y = -1{\cdot}6 - 0{\cdot}141x + 0{\cdot}00981x^2$; SD = 7·58; $r = 0{\cdot}919$.

Results

CRL was measured in 183 fetuses, BPD in 201, HC in 162, AC in 160, femur length in 133 and foot length in 62. Fig. 1 shows the percentage of measurements obtained in relation to the number of fetuses examined at each gestational age. The percentage of fetuses in which CRL was measured decreased, whereas the other measurements were obtained with increasing ease with advancing gestation.

The best description of the relation to CRL to gestational age was achieved by a quadratic function ($y = -3{\cdot}98 - 0{\cdot}308x + 0{\cdot}0117x^2$, $r = 0{\cdot}936$, $P<0{\cdot}0001$).

Mean values thus derived were not statistically different, and actually were nearly identical, to those reported by Robinson & Fleming (1975), once corrected for the effect of beam width, inaccuracies of velocity calibration and errors due to oscilloscope scale factor (Fig. 2).

Fetal BPD, HC, AC and femur length also showed significant correlations with gestational age. However, multiple regression showed this correlation to be independent of CRL for BPD ($P = 0{\cdot}003$), whereas this was not true for HC ($P = 0{\cdot}051$), AC ($P = 0{\cdot}39$) and femur length ($P = 0{\cdot}64$), all of which were significantly correlated only with CRL values (all = $P<0{\cdot}0001$).

Figs. 3–7 show the individual measurements and reference ranges (mean and 95% data intervals) for CRL, BPD, HC, AC and femur length in relation to gestational age. Table 1 displays the means and 95% data intervals for the same fetal measurements in relation to CRL values.

Fetal HC/AC ratio (mean 1·26, SD 0·12) and femur/foot length ratio (mean 0·98, SD 0·16) did not vary significantly with gestational age or CRL.

Discussion

With the exception of a longitudinal study describing the growth of CRL and cephalic pole in 25 women who underwent *in vitro* fertilization and embryo transfer (Bonilla-Musoles *et al* 1988), this is to our knowledge the first study on the size of

Table 1. Means and 95% data intervals of fetal biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and femur length, in relation to crown-rump length (CRL) measurements

	BPD			HC			AC			Femur		
CRL	2·5	Mean	97·5	2·5	Mean	97·5	2·5	Mean	97·5	2·5	Mean	97·5
5	1·9	4·8	7·7	6·5	17·4	28·3	1·6	10·9	20·1		0·2	3·4
15	4·7	7·6	10·5	17·2	28·0	38·8	10·9	20·0	29·2		1·9	5·0
25	7·6	10·5	13·4	27·8	38·5	49·3	20·1	29·2	38·3	0·5	3·6	6·6
35	10·5	13·4	16·2	38·4	49·1	59·8	29·3	38·3	47·3	2·2	5·2	8·2
45	13·4	16·2	19·1	49·0	59·7	70·3	38·5	47·5	56·6	4·0	6·9	9·9
55	16·2	19·1	22·0	59·5	70·2	80·9	47·6	56·7	65·7	5·6	8·5	11·5
65	19·1	22·0	24·8	70·0	80·8	91·6	56·7	65·8	75·0	7·2	10·2	13·2
75	21·9	24·8	27·7	80·4	91·3	102·2	65·8	75·0	84·2	8·8	11·9	15·0
85	24·7	27·7	30·6	90·9	101·9	113·0	74·8	84·1	93·5	10·5	13·5	16·7

All values in mm.

fetal head, trunk and limbs in the first trimester using high resolution transvaginal sonography.

When compared with transabdominal scanning, the transvaginal approach allows improved resolution and high degrees of magnification, but yields a smaller field of vision. This explains the lower success rate in achieving measurements of CRL with advancing gestation. Smaller measurements, such as BPD and HC, were obtained more frequently than CRL after the 11th week. Since the aim at any gestation was to obtain as many fetal measurements as possible, it seems that fetal biometry can be achieved more easily in the late first trimester from measurements other than CRL.

Although all the women had certain menstrual dates, most biometrical measurements correlated better with CRL than with gestational age. This suggests that either a wide range in the day of conception occurs even in women such as these or, alternatively, that genetic or environmental factors already modulate growth in the first trimester. Since head, abdominal and limb growth was mainly related to CRL, the latter measurement may be used as an index of growth as well as of gestational age.

In this respect, previous observations of lower CRL values in insulin dependent diabetic patients (Pedersen & Molsten-Pedersen 1981) may indeed point to delayed growth rather than delayed implantation.

Surprisingly, reference data obtained in 1990 with transvaginal sonography are virtually identical to those produced in 1975 with static scanners, once corrected for the systemic error of the technique (Robinson & Fleming 1975).

During the second and third trimesters, the relation between gestation and cephalic or abdominal measurements is best described by polynomial, logarithmic or exponential equations (Levi & Erbsman 1975; Persson *et al.* 1978; Hadlock *et al.* 1982a & b; Deter *et al.* 1982a & b, 1984; Todros *et al.* 1987). By contrast, in the first trimester, the growth of BPD and HC was best expressed by the simplest function, a linear regression. This may be explained by the fact that a small segment of any curve described by a complex function can always be approximated to a straight line, especially if the time period investigated is limited and the growth rate is fast, as in this case.

The best fit for CRL growth was a quadratic function. Referencing the other measurements to CRL avoids any bias due to variance in conceptional age and individual growth profile, factors which may explain some of the difficulties encountered so far in describing the process of fetal growth.

It is known that femur/foot length ratio does not change with gestation and approximates one in the second and third trimester (Campbell *et al.* 1988). Our study demonstrates that these properties of femur/foot length ratio apply even in the first trimester. On the other hand, our data do not confirm an extention into the first trimester of the second and third trimesters trend of a decrease in the HC/AC ratio with gestation (Campbell & Thoms 1977). Further studies are needed to establish whether this reflects a real difference in the relative pattern of growth between the first and the second trimester fetus.

A benefit of transvaginal sonography is the ability to obtain in the first trimester measurements of fetal growth other than CRL and to compare them with reference ranges such as ours. This would facilitate the assessment of fetuses at risk of genetic disorders affecting growth of the head, trunk or limbs early in fetal life.

References

Bonilla-Musoles F., Perez-Gil M., Barron R., Serra V. & Pardo G. (1988) Transvaginal ultrasound in the first trimester of pregnancy. *Riv Ost Gin* **1**, 247-251.

Bovicelli L., Orsini L. F., Rizzo N., Calderoni P., Pazzaglia F. & Michelacci L. (1981) Estimation of gestational age during the first trimester by real time measurement of fetal crown-rump length and biparietal diameter. *J Clin Ultrasound* **9**, 71-75.

Campbell J. , Henderson A. & Campbell S. (1988) The fetal femur/foot length ratio: A new parameter to assess dysplastic limb reduction. *Obstet Gynecol* **72**, 181-184.

Campbell S. & Newman G. B. (1971) Growth of the fetal biparietal diameter during normal pregnancy. *Br J Obstet Gynaecol* **78**, 513-519.

Campbell S. & Thoms A. (1977) Ultrasound measurement of the fetal head to abdomen circumference ratio in the assessment of growth retardation. *Br J Obstet Gynaecol* **84**, 165-174

Deter R. L., Harrist R. B., Hadlock F. P. & Poindexter A. N. (1982a) Longitudinal studies of fetal growth with the use of dynamic image ultrasonography. *Am J Obstet Gynecol* **143**, 545-554.

Deter R. L., Harrist R B., Hadlock F. P. & Carpenter R. J. (1982b) Fetal head and abdominal circumferences: II. A critical re-evaluation of the relationship to menstrual age. *J Clin Ultrasound* **10**, 365-372.

Deter R. L., Harrist R. B., Hadlock F. P., Cortissoz C. M. & Batten G. W. (1984) Longitudinal studies of fetal growth using volume parameters determined by ultrasound. *J Clin Ultrasound* **12,** 313-324.

Goldstein S. R. (1990) Incorporating endovaginal ultrasonography into the overall gynecologic examination. *Am J Obstet Gynecol* **162,** 625-632.

Green J. J. & Hobbins J. C. (1988) Abdominal ultrasound examination of the first trimester fetus. *Am J Obstet Gynecol* **159,** 165-175.

Hadlock F. P., Deter R. L., Harrist R. B. & Park S K. (1982a) Fetal biparietal diameter: A critical re-evaluation of the relation to menstrual age by means of real-time ultrasound. *J Ultrasound Med* **1,** 145-150.

Hadlock F. P., Deter R. L., Harrist R. B. & Park S. K. (1982b) Fetal head circumference: Relation to menstrual age. *AJR* **138,** 649-653.

Levi S . & Erbsman F. (1975) Antenatal fetal growth from the 19th week: ultrasonic study of 12 head and chest dimensions. *Am J Obstet Gynecol* **121,** 262-268.

Pedersen J. F. & Molsted-Pedersen L. (1981) Early fetal growth delay detected by ultrasound marks increased risk of congenital malformation in diabetic pregnancy. *Br Med J* **283,** 269-271.

Persson P. H., Grennert L., Gennser G. & Gullberg B. (1978) Normal range curves for the intrauterine growth of the biparietal diameter. *Acta Obstet Gynecol Scand* **78** (suppl.), 15-20.

Robinson H. P. (1973) Sonar measurements of the fetal crown-rump length as a mean of assessing maturity in the first trimester of pregnancy. *Br Med J* **iv,** 28-31.

Robinson H. P. & Fleming J. E. E. (1975) A critical evaluation of sonar 'crown-rump length' measurements. *Br J Obstet Gynaecol* **82,** 702-710.

Rottem S., Bronshtein M., Thaler I. & Brendes J. M. (1989) First trimester transvaginal sonographic diagnosis of fetal anomalies. *Lancet* **i,** 444-445.

Royston P. (1991) Constructing time-specific reference ranges. *Stat Med* **10,** 675-690.

Timor-Tritsch I. E., Farine D. & Rosen M. G. (1989) A close look at early embryonic development with the high frequency transvaginal transducer. *Am J Obstet Gynecol* **159,** 676-681.

Todros T., Ferrazzi E., Groli C., *et al.* (1987) Fitting growth curves to head and abdomen measurements of the fetus: A multicentric study. *J Clin Ultrasound* **15,** 95-105.

Received 14 August 1990
Resubmitted 2 April 1991
Accepted 20 August 1991

British Journal of Obstetrics and Gynaecology
January 1992, Vol. 99, pp. 43–45

FETAL AND NEONATAL MEDICINE

In-utero sound levels when vibroacoustic stimulation is applied to the maternal abdomen: an assessment of the possibility of cochlea damage in the fetus

S. ARULKUMARAN
Associate Professor
Department of Obstretrics and Gynaecology,
National University Hospital,
Singapore
D. TALBERT
Senior Lecturer
Institute of Obstetrics and Gynaecology,
Royal Postgraduate Medical School,
Queen Charlotte's & Chelsea Hospital,
Goldhawk Road, London, UK
T. S. HSU
Senior Lecturer
Department of Physics
S. CHUA
Lecturer
C. ANANDAKUMAR
Senior Lecturer
S. S. RATNAM
Professor
Department of Obstetrics and Gynaecology,
National University Hospital,
Singapore.

ABSTRACT

Objective To measure sound pressure level *in utero* while a vibro acoustic stimulator is applied to maternal abdomen and to calculate whether the estimated effect on fetal cochlea cilia vibration would be hazardous.
Design Prospective descriptive study.
Setting Labour ward, National University Hospital, Singapore.
Subjects Eight women undergoing induction of labour.
Intervention A hydrophone was introduced via the cervix into the uterus and placed under ultrasound guidance near the fetal ear. Sound pressure was recorded when a vibroacoustic stimulator was applied directly to the maternal abdomen and also when separated by 2 cm of air.
Main outcome measures Sound pressure levels *in utero*.
Results The sound level recorded from the vibrator diaphragm in air was 107 dB at 2 cm and 74 dB at 1 m. The mean sound pressure level *in utero* was 90·7 dB (range 75–96 dB) when the vibrator was in contact with the abdominal wall and 80·1 dB (range 70–88 dB) when separated by 2 cm of air.
Conclusions Analysis of factors affecting displacement of cochlear sensing cilia *in utero* show that, for equal sound pressures, sound intensity and sound vibration are about 4000 times less in amniotic fluid, compared to that produced in air. Further protection is provided by viscous and hydrodynamic features of the ear. The estimated effect on cilia vibration by the mean sound pressure registered *in utero*, about 90 dB, corresponds to that produced postnatally by an airborne sound registering about 40 dB, which would not be hazardous.

The use of vibroacoustic stimulation of the fetus by an artificial electronic larynx to reduce the number of non-reactive cardiotocographic (CTG) tests has become popular (Smith *et al.* 1985; 1986). However, concern has been expressed regarding possible harmful effects to the fetus (Romero *et al* 1988; Prechtl 1988). This has been highlighted by a report by Gerhardt *et al* (1990) of intrauterine high sound pressure levels in pregnant ewes, measured by a hydrophone, while using a vibroacoustic stimulator. These workers conclude 'To what extent these stimuli penetrate the cochlea and stimulate hair cell activity remains to be determined. Quantification of sound reduction from the sound field of the ewe to the fetal inner ear is important before the likelihood of imprinting and environmental noise hazards can be assumed'.

Fundamental to any consideration of the hazard of excessive sound levels to the fetal ear is the nature of sound itself. Sound results when a fluctuating pressure produces a corresponding fluctuating movement in the medium through which it travels. Hydrophones and most microphones detect the pressure component of sound, and decibel values for sound levels indicate a ratio of measured sound pressure to a reference pressure of 20 μPa r.m.s., just below the threshold of hearing (Kaye & Laby 1982).

Unlike hydrophones and microphones which detect the pressure produced by the sound, the ear detects movement produced in a membraneous structure separating two fluid columns within a common bony enclosure, the cochlea. This ossifies in cartilage in mid-pregnancy (Blasberg & Stool 1977). The cochlea has two sound 'windows', oval and round, connecting the fluid on each side of this structure to the middle ear. Pushing in one window causes the fluid behind it to bend the dividing structure towards the other column, causing its fluid to push the other window outwards. The sensing elements are fine cilia projecting from the principal (basilar) membrane of this structure (Cormack 1987) which are deflected by the fluid movement.

Correspondence: Associate Professor S. Arulkumaran, National University Hospital, Lower Kent Ridge Road, Singapore 0511.

Physical and physiological considerations

In water or body fluids, vibration for a given sound *pressure* is about 1/4000 of that in air (Appendix). The ear would be very insensitive if the windows were directly exposed to the air in the middle ear, the more so because pressures at the two windows would be equal and the cilia would not experience movement. Malleus, incus and stapes form a compound lever system, with a ratio of about 20:1, which partially matches the low pressure/large movement sound in low density air to the high pressure/low movement sound in higher density cochlear fluid. The force created by the airborne sound pressing on the ear drum is increased by 20:1 at the stapes, while stapes movement is 1:20 less than at the eardrum. The stapes acts on the oval window, and the effect is further enhanced by the larger area of the drum compared with that of the oval window. The round window is free to move to release the pressure in the cochlea. The result is displacement of the basilar membrane, shear stressing the cilia of the hair cells, disturbing their cell membranes and causing them to 'fire' (Cormack 1987). These cilia appear to be the most fragile part of the hearing apparatus (Borg & Counter 1989). Rubel *et al.* (1984) found experimentally that damage to these cells was low in prehatch chicks compared with posthatch chicks for the same sound exposure. Cilia appeared to have been broken off by excessive vibration in the posthatch chicks, whereas the prehatch chicks were protected by the fluid filling their ears.

We know of no microphone or hydrophone suitable for *in utero* measurement of sound oscillatory vibration and so vibration was estimated from pressure measurement and the acoustic impedance of the media concerned. A hydrophone was introduced into the amniotic fluid in women in the third trimester and the sound level measured, while a vibro-acoustic stimulator was activated on the maternal abdomen.

Subjects and methods

Patients scheduled for induction of labour in the National University Hospital labour ward were selected for the study. After informed consent artificial rupture of membranes was performed and a hydrophone (Bruel & Kjaer 8103, Denmark), sterilized by immersing in 2% activated glutaraldehyde solution, was introduced through the vagina and cervix into the uterine cavity. Using a portable ultrasound machine (Hitachi EUB 200, Japan) the passage of the hydrophone was guided so that it was close to the lateral aspect of the middle third of the fetal head and as far as possible surrounded by amniotic fluid. The background noise level within the uterus was recorded for 20–30 min.

The sound source was a fetal vibroacoustic stimulator (Corometrics Medical Systems, Connecticut, USA) connected to a locally assembled equipment (Physics Department, National University of Singapore). This produced three broad spectra signals of equal sound pressure, selectable on fundamental frequencies of 55 110 and 220 Hz. The disc of the vibroacoustic stimulator was placed on the maternal abdominal wall over the region of the fetal head and activated for 10 s at each frequency. The noise produced transmitted through the maternal tissue and the amniotic fluid was recorded from the hydrophone. The distance from the vibroacoustic stimulator face to the hydrophone was measured by using a portable ultrasound machine (Hitachi EUB 200). After the background noise was recorded for a further 10 min, the fetal acoustic stimulator was used again as described above but just above the previous point of application, separated from the maternal abdomen by 2 cm of air. At the end of the experiment, the hydrophone was withdrawn from the uterus by gentle traction on the hydrophone cable.

The recording equipment consisted of a Bruel & Kjaer hydrophone 8103, a charge amplifier (Bruel & Kjaer 2635) and a tape recorder (Nagra IV-SJ) with facilities for listening by earphones. The signals were recorded on Maxell UD 35 tapes and analysed by a high resolution signal analyzer (Bruel & Kjaer 2034).

The hydrophone was 25 mm long and 8 mm in diameter, with a frequency response from 0·1 Hz to 125 kHz (± 2 dB). It was calibrated with a hydrophone calibrator (Bruel & Kjaer 4223) at 166 dB and the calibrations were checked before and after the recordings. The sound pressure levels recorded by hydrophone were analyzed to derive the mean and the range.

Results

The sound level recorded in air, directly in front of the vibrator diaphragm, was 107 dB at 2 cm distance and 74 dB at 1000 cm.

Eight women were studied in whom the hydrophone was positioned near the fetal ear, close to the anterior abdominal wall. The vibro-acoustic stimulator was at a mean distance of 4·8 cm (range 3·4–6·2 cm) from the intrauterine hydrophone. The mean and range of sound pressure levels recorded are given in Table 1. Using the stimulator in direct contact with the maternal abdomen, at the standard fundamental frequency of 110 Hz, the mean sound pressure level was 90·7 dB (range 75–96 dB). Holding the stimulator 2 cm above corresponding sites, the mean level was 80·1 dB (range 70–88 dB). The mean background noise *in utero* was 65 dB. Sound levels were not significantly different for the various frequencies used (Table 1).

Table 1. Sound pressure levels in the uterus recorded by hydrophone from a vibroacoustic stimulator held in contact with abdomen or separated by 2 cm of air

		Sound pressure levels (dB) produced by stimulator at median frequencies of					
		55 Hz		110 Hz		220 Hz	
	Background noise *in utero*	Touching	Separated by 2 cm of air	Touching	Separated by 2 cm of air	Touching	Separated by 2 cm of air
Mean	65	87·4	76·3	90·7	80·1	90·1	78·6
Range	60-68	70-90	65-78	75-96	70-88	78-95	68-86

Discussion

All data on sound safety levels assume airborne sound with the malleus/incus/stapes lever mechanism intact. If the experimentally observed mean intrauterine sound pressure level of 90·7 dB, produced by the stimulator in contact, were present in air this would correspond to the cilia vibration caused by a pneumatic drill at 7 m distance. But this sound pressure was measured in a fluid environment, and the fetal outer and middle ears were also fluid filled. The acoustic impedance of amniotic fluid, damping of ossicle lever action, and change of sound pressure distribution to the oval and round windows of the cochlea, all act to reduce vibration sensed by the cilia.

Starting at the eardrum, the vibration due to fluid sound movement is about 1/4000 of that in air for the same sound pressure (Appendix). This means that in amniotic fluid the sound intensity is 36 dB less than it would be in air for the same sound pressure.

Flooding of the middle ear also impairs inner ear function by loading the round window and impeding cochlear pressure release. A somewhat analogous situation is that of conductive hearing loss due to fluid filling in effusive otitis media for which a representative value might be 20 dB (Sweitzer 1977). Adding these two values indicates that fluid vibration around the cilia *in utero* corresponds to a sound level in air 56 dB less than that indicated by sound pressure measurements. Thus if the hydrophone gave an indication of 90 dB after having been calibrated in terms of sound pressure, the cilia would perceive a vibratory displacement corresponding to 90–56 = 34 dB in air. The cilia excursion produced by the vibroacoustic stimulator used in this study would on this basis correspond to that due to normal conversation at 1 m, and would be well below that constituting a hazard.

References

Blasberg B. & Stool S. E. (1977) Developmental and gross anatomy of the ear. In *Hearing Loss in Children* (Jaffe B. F., ed.) University Park Press, Baltimore, London, Tokyo, pp. 3-26.

Borg E. & Counter S. A. (1989) The middle ear muscles. *Sci Am* **8**, 62-68.

Cormack D. H. (1987) The ear. In *Ham's Histology*, 9th ed., Lippincott London, Mexico City, New York, St Louis, Sao Paulo, Sydney, pp. 698-707.

Gerhardt K. J., Abrams R. M. & Oliver C. C. (1990) Sound environment of the fetal sheep. *Am J Obstet Gynecol* **162**, 282-287.

Kaye G. W. C. & Laby T. H. (1982) *Tables of Physical and Chemical Constants and Some Mathematical Functions*, 14th Ed., Longman, London, New York, p. 70.

Prechtl H. F. R. (1988) Developmental neurology of the fetus. *Baillieres Clin Obstet Gynaecol* **2**, 21-35.

Romero R., Mazor M. & Hobbins J. C. (1988) A critical appraisal of fetal acoustic stimulation as an antenatal test for fetal well-being. *Obstet Gynecol* **71**, 781-786.

Rubel E. W., Born D. E., Deitch J. C. & Durham L. (1984) Recent advances toward understanding auditory system development. In *Hearing Science* (Berlin C., ed.), San Diego College, Hill Press, pp. 109-158.

Smith C. J., Phelan J. P., Platt R. H. & Broussard P. (1985) Fetal acoustic stimulation testing· a retrospective experience with the fetal acoustic stimulation test. *Am J Obstet Gynecol* **153**, 567-569.

Smith C. J , Phelan J. P. & Platt L. D (1986) Fetal acoustic stimulation testing II. A randomized clinical comparison with the non-stress test. *Am J Obstet Gynecol* **155**, 131-134.

Sweitzer R. S. (1977) Audiologic evaluation of the infant and young child. In *Hearing Loss in Children* (Jaffe B. F., ed.), University Park Press, Baltimore, London, Tokyo, pp. 101-131.

Wells P. N. T. (1977) Wave fundamentals. In *Biochemical Ultrasonics*. Academic Press, London, New York, San Francisco, pp. 1-25.

Received 3 August 1990
Resubmitted 23 July 1991
Accepted 18 August 1991

Appendix

The relation between sound pressure, acoustic impedance and sound vibratory displacement

The movement caused by sound is difficult to measure accurately because it is extremely small, but it can be related to sound pressure through a property of the material through which the sound is travelling known as acoustic impedance.

Acoustic Impedance (Z) of a material describes how much sound pressure (dP) is required to produce any given vibration velocity (dV) in that material.

$$Z = \frac{dP}{dV} \quad \dots\dots (1)$$

or

$$dV = \frac{dP}{Z} \quad \dots\dots (2)$$

The higher the impedance the less the vibration.

Let Za be the acoustic impedance of air and Zw be that of water; dVa be the vibration velocity in air and dVw that in water. Then if the same sound pressure is applied in the two materials the ratio of their vibrational velocities is the inverse of their impedances.

$$\frac{dVw}{dVa} = \frac{Za}{Zw} \quad \dots\dots (3)$$

from which the proportional change in ciliary motion can be deduced if Za and Zw are known.

It can be shown (Wells 1977) that, for plane waves, impedance is numerically equal to the wave velocity of sound through the medium, c, multiplied by the density of the medium D, (often called rho)

$$Z = D \times c \quad \dots\dots (4)$$

D and c are more easily measured than the vibrational velocities dV, and values are more readily available (Kay & Laby 1982).

The density of air is approximately 1 kg/m^3 and the velocity of sound is about 376 m/s at body temperature.

The density of water is 1000 kg/m^3 and the velocity of sound 1513 m/s.

Substituting the values given by equation (4) in equation (3), the ratio of movements in air and water is therefore:

$$\frac{dVw}{dVa} = \frac{(1 \times 376)}{(1000 \times 1513)} = \frac{1}{4024}$$

i.e., vibration is approximately 4000 times less in water than in air at body temperature and for the same sound pressure.

Sound intensity is a measure of the rate at which energy is being transferred through unit area, and is proportional to the product dP.dV. When comparing sounds of equal pressure (dP) components in the two media, energy transferred is proportional to their velocity components (dV), and therefore in the same ratio.

British Journal of Obstetrics and Gynaecology
January 1992, Vol. 99, pp. 46–50

FETAL AND NEONATAL MEDICINE

Fetal urine biochemistry: an index of renal maturation and dysfunction

UMBERTO NICOLINI
Senior Lecturer/Consultant
NICHOLAS M. FISK
Hon. Lecturer/Senior Registrar
CHARLES H. RODECK
Professor

Royal Postgraduate Medical School,
Institute of Obstetrics and
Gynaecology, Queen Charlotte's and
Chelsea Hospital, Goldhawk Road,
London W6 0XG

JEREMY BEACHAM
Principal Scientific Officer

Royal Postgraduate Medical School,
Department of Chemical Pathology,
Hammersmith Hospital, Du Cane
Road, London W12 0NN

ABSTRACT

Objective To construct a reference range for fetal urinary sodium, potassium, urea, creatinine, calcium and phosphate with gestation and to assess to what extent these biochemical indices are modified in fetuses with lower urinary tract obstruction.
Design Prospective descriptive study.
Setting Royal Postgraduate Medical School London.
Subjects 24 women between 17 and 35 weeks gestation with an ultrasound diagnosis of fetal lower urinary tract obstruction, with or without renal dysplasia and a control group of 26 women between 16 and 33 weeks gestation with normal amniotic fluid volume and fetal anatomy.
Interventions Fetal urine samples (1–100 ml) were aspirated from the control fetuses either before termination of pregnancy ($n = 9$) or at the time of intrauterine transfusion for Rh alloimmunization ($n = 17$). The fetuses with obstructive uropathy had urine samples aspirated on one occasion ($n = 14$) or serially ($n = 10$).
Main outcome measures Relation between urine biochemistry and renal damage ascertained clinically or at postmortem.
Results In the control group, urinary sodium and phosphate decreased and creatinine increased significantly with gestational age, consistent with increasing fetal glomerular filtration rate and progressive maturation of tubular function. Urinary sodium and calcium were significantly higher in fetuses with renal dysplasia compared with those with lower urinary tract obstruction but normal renal histology or normal clinical outcome. Serial urinary samples from fetuses with obstructive uropathy showed more pronounced deviation from the normal with increasing gestation in all fetuses with renal dysplasia. The highest sensitivity in the detection of renal dysplasia was shown by urinary calcium (100%) whereas urinary sodium showed the best specificity (80%).
Conclusion Renal damage is the direct effect of urinary obstruction, rather than an association so that treatment should start as soon as possible. Urine biochemistry may be helpful in the management of these patients.

Lower urinary tract obstruction in the fetus is associated with poor perinatal outcome (Reuss *et al* 1988). Antenatal treatment, in the form of either vesico-amniotic shunting or. in selected pregnancies, open fetal surgery at hysterotomy, has yielded discouraging results: of 73 pregnancies reported to an international registry, perinatal survival was only 41% (Manning *et al.* 1986). Accordingly, the benefit of intrauterine shunting has been questioned (Elder *et al.* 1987), despite animal studies demonstrating that early urinary decompression prevents lung hypoplasia and renal dysplasia (Glick *et al.* 1984), the two main causes of neonatal death. Furthermore, it has been suggested that renal damage may be associated with, but it is not the direct result of, urinary obstruction (Henneberry & Stephens 1980).

Careful selection of pregnancies for prenatal treatment is crucial (Nicolini *et al.* 1987a). Once other abnormalities have been excluded, the degree of renal damage is the major determinant of outcome. Renal function that is normal at the time of prenatal surgery indicates not only the absence of significant renal damage, but also that, following relief of the obstruction, urine output should restore amniotic fluid volume, thus preventing pulmonary hypoplasia.

The investigation of renal function is far from standardized. Oligohydramnios is a poor prognostic sign, but is related more to the degree of obstruction than to urine production. The ultrasonic appearance of fetal kidneys (cortical cysts, parenchymal hyperechogenicity) has poor sensitivity and specificity (Mahony *et al.* 1984). Determination of electrolytes in fetal urine aspirated from bladder or kidneys has been recommended by some groups and, although now widely used, conflicting results have been reported (Golbus *et al.* 1985; Nicolini *et al.* 1987a; Wilkins *et al.* 1987; Grannum *et al.* 1989; Crombleholme *et al.* 1990). False positive and negative results of urinary electrolytes may be partly explained by several factors:

Correspondence: Umberto Nicolini, II Clinica Ost-Gin, Universita' di Milano, via Commenda 12, 20122 Milano, Italy.

(i) the threshold between abnormal and normal has been established retrospectively from fetuses with obstructive uropathy and good or bad outcome rather than from normal fetuses; (ii) gestational age has not been taken into account, on the assumption that these measurements do not change during pregnancy; (iii) the correlation with histology or clinical outcome has been assessed at varying intervals from the time of intrauterine urine sampling: this implies that no change in the degree of renal damage had occurred with time despite persistance of the obstruction.

The aim of this study was to construct a reference range of biochemical indices in fetal urine with gestation and to assess to what extent they are modified in lower urinary tract obstruction with or without renal cystic dysplasia.

Subjects and methods

A urine sample was obtained from 26 control fetuses and 24 fetuses (25 kidneys) with lower urinary tract obstruction. Gestational age ranged from 16 to 33 weeks in the control group and 17 to 35 in the pregnancies with obstructive uropathy.

Samples of fetal urine (1–100 ml) were obtained using a 20 gauge spinal needle introduced under ultrasonic guidance into the fetal bladder or (in one fetus with obstructive uropathy) into each dilated renal pelvis. Blood-stained samples were discarded.

The control group included nine women who gave informed consent to fetal urine aspiration before termination of pregnancy for social reasons, as approved by the hospital ethics committee, and 17 pregnancies treated by combined intravascular and intraperitoneal transfusion for Rh alloimmunization. The bladder was emptied, before intraperitoneal transfusion, to reduce fetal intra-abdominal volume to minimize the expected increase in intra-abdominal pressure (Nicolini *et al.* 1989). None had abnormalities of amniotic fluid volume or of fetal anatomy. Fetal urine was obtained in the Rh patients at the second to fourth intrauterine transfusion and fetal haemoglobin was always >4 g/dl, the level below which fetal hypoxia may occur (Soothill *et al* 1987). All the fetuses were born after 32 weeks gestation with a normal neonatal course.

All 24 fetuses with lower urinary tract obstruction were shown, either clinically or at postmortem examination, to have posterior urethral valves or urethral atresia. Four had associated anomalies, diagnosed prenatally, two were chromosomal abnormalities (trisomy 18 and inversion of chromosome 6) and two structural (cardiac defect and congenital adenomatoid malformation of the lung type III). Sonographically, the bladder was enlarged in all fetuses, bilateral hydroureter was present in 21, bilateral hydronephrosis in 10 and in 12 the renal parenchyma appeared to have varying degree of hyperechogenicity. Amniotic fluid was markedly reduced in 17 of the pregnancies, normal in four and slightly increased in the remaining three. A vesicoamniotic shunt was inserted in eight fetuses, in two of these the women subsequently decided to have termination of the pregancy in view of the poor prognosis suggested by inadequate reacculumation of amniotic fluid; one patient miscarried a few days after shunt placement; two immediate neonatal deaths occurred due to pulmonary hypoplasia; the remaining three babies are alive and well after postnatal surgical correction of their urinary obstruction.

Our aim was to investigate the relation between urine biochemistry and fetal renal damage. Of the 24 fetuses with lower urinary tract obstruction, 16 had both a urine sample within four weeks of pregnancy ending in termination, miscarriage or neonatal death and also histological examination by experienced histopathologists. Bilateral cystic dysplasia was demonstrated in 12 of these 16 fetuses and excluded in four. In seven fetuses histology was not obtained and urine was sampled 1–15 weeks before delivery; five of these babies are alive without signs of renal failure at 5–20 months, one is being dialysed while awaiting renal transplantation and one died immediately after birth with the typical features of Potter's syndrome. In the remaining fetus, urine was collected from each renal pelvis: the infant is alive and well aged 2, but he underwent unilateral nephrectomy with histological confirmation of dysplasia (Nicolini *et al.* 1987a).

Fourteen fetuses had a single urine aspiration; of the 10 fetuses who provided serial samples, five later proved to have renal cystic dysplasia and in five this was ruled out.

For all fetuses, concentrations of the following urinary variables were determined: sodium (Na^+), potassium (K^+), urea, creatinine, calcium (Ca^{2+}) phosphate (PO_4^{2-}).

The relation of each of these variables to gestational age was assessed in the 26 control fetuses and reference ranges constructed: the Shapiro-Francia W' test was used to check the normality of distribution and determine the optimal transformation required; after allowing for unequal variability at different gestational ages, 95% data intervals (±1·96 SD) were calculated (Royston 1991). All variables were normally distributed, with the exception of Ca^{2+}, for which a logarithmic transformation was used.

Urinary variables in the last sample obtained from fetuses with lower urinary tract obstruction were then compared to the reference ranges and sensitivity and specificity calculated for each. To allow comparisons between fetuses with and without renal dysplasia, independent of gestational age, those variables which correlated significantly with gestation were expressed as number of SDs from the mean of the control group.

Statistical comparisons were made using Student's *t* or the Mann-Whitney *U* tests, as appropriate.

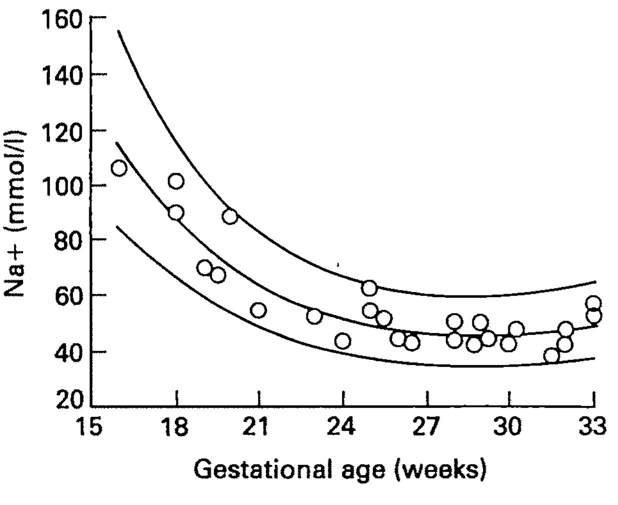


Fig. 1. Mean and 95% data intervals of fetal urinary sodium throughout gestation.

Table 1. Fetal urinary constituents in controls and fetuses with obstructive uropathy

	Na^+ (SD from the mean)	K^+ (mmol/l)	Ca^{2+} (mmol/l)	PO_4^{2-} (SD from the mean)	Urea (μmol/l)	Creatinine (SD from the mean)
Controls ($n = 26$)	0·0 (−0·3 to 0·4)	3·0 (2·4 to 3·7)	0·2 (0·1 to 1·3)	0·0 (−0·3 to 0·4)	7·9 (6·8 to 8·9)	0·0 (−0·4 to 0·4)
	$P<0{\cdot}0001$	$P<0{\cdot}01$	$P<0{\cdot}0001$	$P<0{\cdot}0001$	$P<0{\cdot}0001$	ns
Dysplastic kidneys ($n = 15$)	4·2 (3·1 to 5·3)	4·2 (3·6 to 4·9)	2·0 (1·2 to 2·9)	2·1 (1·2 to 2·9)	4·9 (3·5 to 6·4)	−0·3 (−1·1 to 0·5)
	$P<0{\cdot}001$	ns	$P<0{\cdot}002$	ns	ns	ns
Non-dysplastic kidneys ($n = 10$)	0·6 (−0·5 to 1·8)	3·3 (2·4 to 4·1)	1·2 (0·1 to 1·9)	1·1 (−0·5 to 2·6)	4·3 (2·5 to 6·2)	0·9 (−0·4 to 2·2)

Controls *vs* non-dysplastic kidneys Na^+ = ns, K^+ = ns, Ca^{2+} = $P<0{\cdot}002$, PO_4^{2-} = ns; urea = $P<0{\cdot}01$, creatinine = ns

Results are means (95% CI) values or median (range) values for Ca^{2+}

Results

In the control group, urinary Na^+ decreased significantly with gestational age ($\log y = 3{\cdot}69 - 0{\cdot}141\,x + 0{\cdot}00243\,x^2$, $SD = 0{\cdot}055$, $r = 0{\cdot}91$, $P<0{\cdot}001$) (Fig. 1). Urinary PO_4^{2-} decreased ($y = 1{\cdot}68 - 0{\cdot}048\,x$, $SD = 0{\cdot}33$, $r = -0{\cdot}62$, $P<0{\cdot}001$) from a mean value of 0·91 mmol/l at 16 weeks to a mean of 0·10 mmol/l at 33 weeks gestation. Mean creatinine increased from 99·9 μmol/l at 16 weeks to 172·9 μmol/l at 33 weeks ($y = 31{\cdot}2 + 4{\cdot}29\,x$, $SD = 39{\cdot}5$, $r = 0{\cdot}51$, $P<0{\cdot}001$). The ratio of Na^+ to creatinine showed a significant negative correlation with gestation ($y = 1{\cdot}45 - 0{\cdot}038\,x$, $SD = 0{\cdot}17$, $r = -0{\cdot}77$, $P<0{\cdot}001$). Conversely, K^+ ($r = 0{\cdot}21$), Ca^{2+} ($r = 0{\cdot}18$) and urea ($r = 0{\cdot}06$) did not show any significant correlation with gestational age; mean and 95% data intervals were 3·0 (0–6·1) mmol/l, 0·21 (0·04–1·2) mmol/l and 7·9 (2·6–13·1) μmol/l respectively.

Table 1 shows differences in urinary biochemistry between control fetuses and those with obstructive uropathy, with or without renal dysplasia. The three groups had similar values of creatinine. Fetuses with obstructive uropathy had significantly decreased urea and increased Ca^{2+}, independent of the presence or absence of renal dysplasia, whereas urinary Na^+, K^+ and PO_4^{2-} were higher than in controls only in the presence of renal dysplasia.

In Figure 2 the values of urinary Na^+ from fetuses with obstructive uropathy are plotted against the reference range for gestation. Thirteen of 15 fetuses with renal dysplasia had urinary Na^+ above the upper limit of normal; conversely, 8 of 10 without dysplasia had normal values. Four fetuses with dysplasia had values below 100 mmol/l (the previously accepted threshold) (Glick *et al.* 1985), while one with normal histology had urinary Na^+ above this value. The values of urinary Na^+ in the 10 fetuses sampled serially are shown in Figure 3. There was a more pronounced deviation from the normal with increasing gestation in all five fetuses with renal dysplasia, but also in 1 of the 5 with a normal outcome after subsequent intrauterine shunting.

Table 2 shows the value of urinary Na^+, Ca^{2+} and PO_4^{2-} above or within the reference range in the prediction of renal dysplasia. The highest sensitivity was achieved by the use of urinary Ca^{2+}, which, however, had the lowest specificity. The remaining urinary variables had extremely low sensitivities,

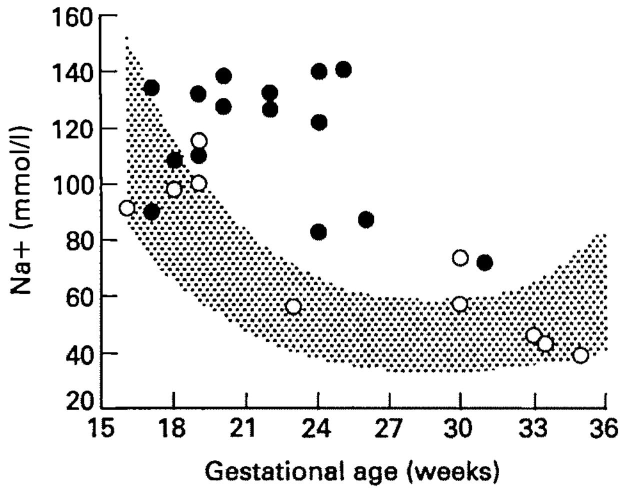


Fig. 2. Urinary sodium in fetuses with lower urinary tract obstruction plotted against the reference range (●) fetuses with renal dysplasia; (○) fetuses without renal dysplasia.

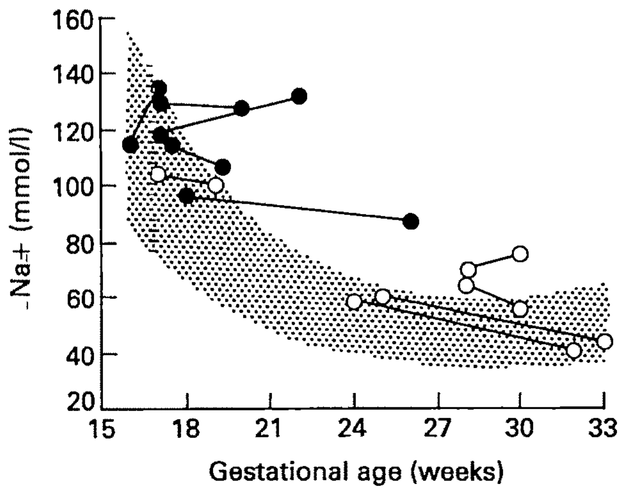


Fig. 3. Urinary sodium in serial samples from fetuses with lower urinary tract obstruction, (●) fetuses with renal dysplasia; (○) fetuses without renal dysplasia.

urea was normal in all fetuses with lower urinary tract obstruction; K^+ was elevated in only two with renal dysplasia and creatinine was below reference limits in one with renal dysplasia and above the reference range in 6 (2 with dysplasia and 4 without).

Discussion

Fetal renal function has, in the past, been investigated mainly through indirect methods. Ultrasonographic studies of renal dimensions (Grannum *et al.* 1980) and hourly urine production rate, as assessed by serial changes in bladder volume (Wladimiroff & Campbell 1974), have suggested that increases in renal size and urinary production with gestation are linear phenomena. Indeed, glomerular filtration rate (GFR), when standardized for body or kidney weight, remains constant throughout gestation in fetal lamb (Robillard *et al.* 1975). On the other hand, human data from preterm newborns show that GFR per kg of body weight increases after 34 weeks, when nephrogenesis is complete (Arant 1978).

Although it is known, from studying fetuses just before termination of pregnancy, that the fetal kidney is capable of reabsorbing Na^+ and excreting urea from as early as 12 weeks (Lind 1981), our understanding of the evolution of fetal renal function is largely inferred from changes in the biochemistry of amniotic fluid, the volume of which, at least in the second half of gestation, is largely dependent on fetal micturition. The rise in amniotic fluid urea and creatinine and the fall in Na^+ and osmolarity (Lind 1981) suggest both an increase in fetal GFR and progressive maturation of tubular function with advancing gestation.

Although some creatinine is secreted by the tubules and some reabsorbed, most creatinine is simply filtered by the glomerulus. Therefore, the linear increase in creatinine concentration that we found in fetal urine could be considered to reflect an increase in GFR, provided that reabsorption of water and solutes remains constant. This, however, seems unlikely, in view of the urinary Na^+ concentration, an index of tubular reabsorption, falling with gestation faster than the increase in creatinine. On the other hand, parallel maturation of both GFR and tubular function is suggested by our finding of no change with gestation in the urinary concentration of urea, which, with approximately 50% being reabsorbed in the tubules, is dependent on both renal mechanisms.

The remaining electrolytes studied (K^+, Ca^{2+}, PO_4^{2-}) largely reflect tubular function. Since K^+ is both reabsorbed and secreted by the tubule, its constant concentration in urine, as pregnancy advances, may be explained by maturation of both aspects of tubular function. Conversely, Ca^{2+} and PO_4^{2-} are subject to tubular reabsorption only. The difference between Ca^{2+}, which did not change significantly, and PO_4^{2-}, which decreased progressively with gestation, remains unexplained.

In the adult, 98–99% of filtered Na^+ and Ca^{2+} is reabsorbed by the tubules. The highest sensitivity in the detection of renal dysplasia due to urinary obstruction was achieved by these two electrolytes. This indicates that tubular rather than glomerular damage occurs in the earlier stages of obstructive nephropathy.

The higher sensitivity, but lower specificity of Ca^{2+}, together with different trends with gestation in urinary Na^+ and Ca^{2+}, suggest that the maximal reabsorption of Ca^{2+} occurs at an earlier stage of pregnancy, that is this function matures more rapidly than reabsorption of Na^+. The small numbers in this study do not permit sub-analysis of accuracy at varying gestational ages, but greater accuracy of urinary Na^+ would, on this basis, be expected in later rather than earlier pregnancy.

Table 2. Sensitivity and specificity of urinary sodium (Na^+), calcium (Ca^{2+}) and phosphate (PO_4^{2-}) in the prediction of renal dysplasia within the group of fetuses with obstructive uropathy

	Sensitivity	Specificity
Na^+	87% (13/15)	80% (8/10)
Ca^{2+}	100% (15/15)	60% (6/10)
PO_4^{2-}	53% (8/15)	62% (5/8)

If the widely adopted threshold of 100 mmol/l for urinary Na^+ (Glick *et al.* 1985; Crombleholme *et al* 1990) had been used in our series, 27% of the fetuses with dysplasia would have been classified as having normal renal function. Such a low sensitivity is in agreement with data from a series of nine fetuses reported by Wilkins *et al.* (1987), but contrasts with another study (Grannum *et al.* 1989). Gestational age at urine aspiration may account for these discrepancies: from our data, a value of 100 mmol/l is normal at 16–20 weeks, whereas, after 24 weeks, values as low as 70–80 mmol/l may be associated with renal dysplasia.

Although there was a significant difference between fetuses with and without renal dysplasia in urinary concentrations of Na^+ and Ca^{2+}, there was still a degree of overlap between the two groups for both constituents. Despite normal histology, fetuses with lower urinary tract obstruction without dysplasia tended to have minor abnormalities of those urinary variables reflecting tubular function, although most of these were still within the reference range. This is consistent with a degree of impairment of tubular function secondary to the obstruction itself. Conversely, since creatinine, the variable mainly reflecting GFR, was seldom abnormal, GFR does not appear to be compromised, except in very severe renal dysplasia. This concept is further supported by the occurrence of increased, rather than decreased, amniotic fluid volume in some cases of incomplete urinary tract obstruction (Nicolini *et al.* 1987b).

The understanding of normal fetal renal physiology is a prerequisite when facing the problem of fetal obstructive uropathy. Prenatal surgery, although controversial, does have a role in selected pregnancies (Longaker *et al.* 1989; Crombleholme *et al.* 1990). Most of the scepticism about the procedure is the result of poor selection of fetuses which may benefit from prenatal treatment.

We acknowledge that sampling of fetal urine is still associated with diagnostic pitfalls and do not completely accept the optimistic view of other authors (Grannum *et al.* 1989). However, our data, showing worsening renal function on serial urine samples in fetuses later demonstrated to have renal dysplasia, support the view that renal damage is the direct effect of urinary obstruction, rather than an association. In this respect, the gestation at which treatment is started should be crucial.

The use of these reference ranges for urinary biochemistry may prove helpful in the future management of these patients.

Acknowledgments

N.M.F. was supported by a Joseph Foreman Fellowship from Royal Prince Alfred Hospital, Sydney, Australia.

References

Arant B. S. (1978) Development patterns of renal functional maturation compared in the neonate. *J Pediatr* **92,** 705-712.

Crombleholme T. M , Harrison M. R., Golbus M. S., *et al* et al. (1990) Fetal intervention in obstructive uropathy. prognostic indicators and efficacy of intervention. *Am J Obstet Gynecol* **162,** 1239-1244.

Elder J. S., Duckett J. W. Jr. & Snyder H. M. (1987) Intervention for fetal obstructive uropathy: has it been effective? *Lancet* **ii,** 1007-1010.

Glick P. L., Harrison M. R., Adzick N. S., Noall R. A. & Villa R. L. (1984) Correction of congenital hydronephrosis in utero IV: in utero decompression prevents renal dysplasia. *J Pediatr Surg* **19,** 649-657.

Glick P.L., Harrison M. R., Golbus M. S., *et al* (1985) Management of the fetus with congenital hydronephrosis II: prognostic criteria and selection for treatment. *J Pediatr Surg* **20,** 376-387.

Golbus M. S., Filly R. A., Callen P. W., Glick P. L., Harrison M .R. & Anderson R. L. (1985) Fetal urinary tract obstruction: management and selection for treatment. *Semin Perinatol* **9,** 91-97.

Grannum P., Bracken M., Silverman R. & Hobbins J. C. (1980) Assessment of fetal kidney size in normal gestation by comparison of kidney circumference to abdominal circumference. *Am J Obstet Gynecol* **136,** 249-254.

Grannum P. A., Ghidini A , Scioscia A., Copel J. A., Romero R. & Hobbins J. C. (1989) Assessment of fetal renal reserve in low level obstructive uropathy. *Lancet* **i,** 281-282.

Henneberry M. O. & Stephens F. D. (1980) Renal hypoplasia and dysplasia in infants with posterior urethral valves. *J Urol* **123,** 912-915.

Lind T. (1981) The biochemistry of amniotic fluid. In *Amniotic Fluid and Its Clinical Significance.* (Sandler M., ed.), Dekker Inc., New York and Basel, pp. 1-25.

Longaker M. T., Adzick N. S. & Harrison M. R. (1989) Fetal obstructive uropathy. *Br Med J* **299,** 325-326.

Mahony B. S., Filly R. A., Callen P. W., Hricak H., Golbus M. S. & Harrison M. R. (1984) Sonographic evaluation of fetal renal dysplasia. *Radiology* **152,** 143-146.

Manning F. A., Harrison M. R. & Rodeck C. H. (1986) Catheter shunts for fetal hydronephrosis and hydrocephalus. *N Engl J Med* **315,** 336-340.

Nicolini U., Rodeck C. H. & Fisk N. M. (1987a) Shunt treatment for fetal obstructive uropathy. *Lancet* **ii,** 1338-1339.

Nicolini U., Ferrazzi E., Kustermann A., *et al.* (1987b) Perinatal management of fetal hydronephrosis with normal bladder. *J Perinat Med* **15,** 53-60.

Nicolini U., Talbert D. G., Fisk N. M. & Rodeck C. H. (1989) Pathophysiology of pressure changes during intrauterine transfusion. *Am J Obstet Gynecol* **160,** 1139-1145.

Reuss A., Wladimiroff J. W., Stewart P. A. & Scholtmeijer R. J. (1988) Non-invasive management of fetal obstructive uropathy. *Lancet* **ii,** 949-951.

Robillard J. E., Kulvinskas C., Sessions C., *et al.* (1975) Maturational changes in the fetal glomerular filtration rate. *Am J Obstet Gynecol* **122,** 601-606.

Royston P. (1991) Constructing time-specific reference ranges. *Stat Med* **10,** 675-690.

Soothill P. W., Nicolaides K. H., Rodeck C. H., Clewell W. H & Lindridge J. (1987) Relationship of fetal hemoglobin and oxygen content to lactate concentration in Rh isoimmunized pregnancies. *Obstet Gynecol* **69,** 268-271.

Wilkins I. A., Chitkara U., Lynch L., Golberg J. D., Mehalek K. E. & Berkowitz R. L. (1987) The non predictive value of fetal urinary electrolytes: preliminary report of outcomes and correlations with pathologic diagnosis. *Am J Obstet Gynecol* **157,** 694-698.

Wladimiroff J. W. & Campbell S. (1974) Fetal urine-production rates in normal and complicated pregnancy *Lancet* **i,** 151-154.

Received 26 June 1990
Resubmitted 9 January 1991
Accepted 20 August 1991

British Journal of Obstetrics and Gynaecology
January 1992, Vol. 99, pp. 51–53

FETAL AND NEONATAL MEDICINE

Maternal serum unconjugated oestriol and human chorionic gonadotrophin levels in pregnancies with insulin-dependent diabetes: implications for screening for Down's syndrome

NICHOLAS J. WALD
HOWARD S. CUCKLE*
JAMES W. DENSEM
ROSSANA B. STONE

Department of Environmental and
Preventive Medicine,
St Bartholomew's Hospital Medical
College, Charterhouse Square, London
EC1M 6BQ

ABSTRACT

Objective To investigate maternal serum unconjugated oestriol (uE_3) and human chorionic gonadotrophin (hCG) levels in pregnant women with insulin-dependent diabetes mellitus and to consider the implications of the results for antenatal screening for Down's syndrome.

Design Descriptive study using stored antenatal serum samples.

Setting Stored serum samples collected from women receiving routine antenatal care in Oxford.

Subjects 126 singleton pregnancies in 92 women with insulin-dependent diabetes mellitus and for each pregnancy, two pregnancies without diabetes matched for gestational age and duration of storage of the serum sample. None of the pregnancies was associated with fetal neural tube defect or Down's syndrome.

Main study measures Maternal serum uE_3 and hCG levels at 15–22 weeks gestation. Alpha-fetoprotein (AFP) levels were also measured for comparison.

Results The median uE_3 level in the diabetic pregnancies was 0·92 multiples of the median (MoM) for pregnancies without diabetes at the same gestational age ($P<0{\cdot}05$); and the hCG level was 0·95 MoM ($P = 0{\cdot}48$). The median AFP level was also reduced to 0·77 MoM ($P<0{\cdot}001$).

Conclusion The reduction in uE_3 and AFP levels in insulin-dependent diabetic pregnancies is sufficiently great to be taken into account in maternal serum screening programmes for Down's syndrome. Dividing the uE_3 and AFP levels in such pregnancies by the corresponding median for insulin-dependent diabetic pregnancies will yield a similar false-positive rate in pregnancies with and without insulin-dependent diabetes mellitus.

Early second trimester maternal serum alpha-fetoprotein (AFP) levels are lower in women with insulin-dependent diabetes mellitus than in women without diabetes, and this has important implications for antenatal screening for neural-tube defects and Down's syndrome (Wald *et al.* 1979; Milunsky *et al.* 1982; Reece *et al.* 1987; Greene *et al.* 1988; Cuckle & Wald 1990). Maternal serum unconjugated oestriol (uE_3) and human chorionic gonadotrophin (hCG) are, with AFP, used to screen for Down's syndrome (Wald *et al.* 1988) and if levels of these two markers are, on average, materially different in women with and without insulin-dependent diabetes mellitus this would also be of importance in screening. We therefore conducted a study to investigate this further using a bank of antenatal serum samples, measuring AFP as well as uE_3 and hCG.

Subjects and methods

We identified 126 singleton pregnancies in 92 women with insulin-dependent diabetes mellitus who attended for their antenatal care at the John Radcliffe Hospital, Oxford between 1975 and 1983 and from whom a serum sample had been collected between 15 and 22 weeks gestation (when Down's syndrome screening usually takes place) and stored at –40°C. The pregnancies were the same as those that we had studied previously in our earlier reports on serum AFP and diabetes (Wald *et al.* 1979; Cuckle & Wald 1990) but restricted to the women who had provided a blood sample between 15 and 22 weeks gestation. The numbers at each completed week of gestation were, respectively, 8, 43, 30, 22, 12, 6, 3 and 2. For each diabetic pregnancy two control singleton pregnancies were selected matching for gestational age (same completed week of pregnancy) and duration of sample storage (same calendar quarter). Serum samples were retrieved from storage and assayed for uE_3 using a direct non-extraction radioimmunoassay (Amerlex oestriol RIA Kit, Amersham), for hCG using

---

Correspondence: N. J. Wald.

*Present address: Department of Obstetrics and Gynaecology, St James's University Hospital, Leeds LS9 7TF.

an immunoradiometric assay (MAIA—Clone Kit, Serono) and for AFP using a radioimmunoassay (North East Thames Radio-immunoassay); the assays were carried out without knowledge of whether the samples were from diabetic or control pregnancies. None of the pregnancies was associated with fetal Down's syndrome or neural tube defect. Only one serum sample was included from each pregnancy. Results were expressed as multiples of the median (MoM) value for non-diabetic pregnancies of the same gestational age (based on 'dates'): normal medians were obtained by regression in the controls. Gestational age was estimated from the first day of the last menstrual period.

The parameters of the distributions of log MoM values were derived as described previously (Wald *et al.* 1991): standard deviation from 90th–10th centile interval divided by 2·563; correlation coefficients after excluding four diabetic and six control pregnancies with extremely outlying values (≥3·5 SD from the median).

Results and Discussion

Table 1 shows the 10th, median and 90th centile of serum uE$_3$, hCG and AFP for the insulin-dependent diabetic pregnancies and the control pregnancies. The median maternal serum uE$_3$ level in the diabetic pregnancies was 0·92 MoM, a small but statistically significant reduction compared with the controls (95% CI 0·85–0·995 MoM). The median hCG level in the diabetic pregnancies was reduced to a similar extent (0·95 MoM) but this was not statistically significant (95% CI 0·81–1·10). The median AFP level in the diabetic pregnancies was 0·77 MoM (95% CI 0·67–0·88 MoM), the same value as that obtained in our previous analysis of all studies combined, which included the pregnancies described in this paper but was based on the AFP results determined while the women were pregnant rather than those obtained from stored samples (Cuckle & Wald 1990).

Table 1. Maternal serum unconjugated oestriol (uE$_3$), human chorionic gonadotrophin (hCG) and alpha-fetoprotein (AFP) levels (in MoMs) among singleton insulin-dependent diabetic pregnancies and control pregnancies between 15 and 22 weeks gestation*

Serum marker	Centile	Insulin-dependent diabetic pregnancies (n = 126) [a]	Control pregnancies (n = 252) [b]	[a/b]
uE$_3$	10th	0·59	0·68	0·87
	Median	0·92	1·00	0·92
	90th	1·26	1·35	0·93
hCG	10th	0·43	0·48	0·90
	Median	0·95	1·01	0·94
	90th	1·87	2·09	0·89
AFP	10th	0·34	0·60	0·57
	Median	0·77	1·01	0·76
	90th	1·39	1·65	0·84

*The difference between diabetic and control pregnancies was tested for statistical significance by calculating a z score for the difference in the median: P = 0·04, for uE$_3$, P = 0·48 for hCG and P <0·001 for AFP.

MoM = Multiple of the median for the control pregnancies at the same gestational age.

Plasma total oestriol levels in insulin-dependent diabetic pregnancies have been reported, mainly in the third trimester, based on small numbers and with varying results. For example Nachtigall *et al.* (1968) and Taylor (1970) found normal levels whereas Levitz & Selinger (1970) reported high values and Masson & Sutherland (1973) found low values. Canick *et al.* (1990), like us, measured uE$_3$ in the second trimester in 24 women with insulin-dependent diabetes mellitus; the median value was 0·87 MoM, similar to our estimate of 0·92 MoM.

Aubry & Nesbit (1970) reported normal hCG levels in diabetic pregnancies. Crosignani *et al.* (1974) obtained similar results but noted high levels if the diabetes was severe and poorly controlled. Two studies found hCG levels to be high on average in diabetics (Selenkow *et al.* 1971; Stewart *et al.* 1989). The median hCG level in the 24 diabetic pregnancies studied by Canick *et al.* (1990) in Rhode Island was low at 0·87 MoM, similar to our estimate of 0·94 MoM and like our results the decrease was not statistically significant. If hCG levels are abnormal in diabetic pregnancies, much larger numbers would be needed to determine this.

Although maternal serum uE$_3$ and AFP levels are, on average, low in women with insulin-dependent diabetes the SD of log values is not materially different from that in non-diabetics (see Table 1 which shows that the ratio of the 10th and 90th centiles in the diabetics and controls was similar to the ratio of the medians). Also the correlation coefficients of the log values were not materially different in the two groups (AFP-uE$_3$ 0·25 and 0·15, P = 0·35; AFP-hCG 0·05 and 0·21, P = 0·14; uE$_3$-hCG −0·04 and −0·13, P = 0·45 using Fisher's z transformation to test the difference). The similarity has useful implications for serum screening for Down's syndrome in which each woman is given a risk of having an affected pregnancy and those with a risk estimate equal to or greater than a specified cut-off level are classified as screen-positive. It means that if, in an insulin-dependent diabetic pregnancy, the uE$_3$ and AFP MoM values were adjusted by dividing them by the mean MoM values in such pregnancies and the woman's risk estimated as if she were not a diabetic, the false-positive rate would, in expectation, be similar to that in non-diabetics. Although estimating the risk in this way is a valid way of judging whether a result is positive, it is not the woman's true risk. Neither this nor the corresponding detection rate can be estimated because the distribution of the maternal serum markers in insulin-dependent diabetic pregnancies with Down's syndrome are not known. The adjustment procedure simply ensures that a similar false-positive rate is maintained in diabetic and non-diabetic pregnancies as we have proposed with twins (Wald *et al* 1991).

Acknowledgment

We thank Professor T. Chard for supplying the reagents used for the AFP assay.

References

Aubry R. H. & Nesbit R. E. L. (1970) Cytohormonal evaluations and their practical utility in managing high-risk patients. *Am J Obstet Gynecol* **107**, 48-64.

Canick J. A., Panizza D. S. & Palomaki G. E. (1990) Prenatal screening for Down syndrome using AFP, uE$_3$, and hCG: Effect of maternal race insulin-dependent diabetes and twin pregnancy. *Am J Hum Genetics* **47** (3), A270.

Cohen M., Haour F., Dumont M. & Bertrand J. (1973) Value of hCG and hCS measurement in clinical practice. *Am J Obstet Gynecol* **115**, 202-210.

Crosignani P. G., Trojsi L., Attanasio A. E. M. & Lombroso Finzi G. C. (1974) Value of hCG and hCS measurement in clinical practice. *Obstet Gynecol* **44**, 673-681.

Cuckle H. S. & Wald N. J. (1990) Screening for Down syndrome. In *Prenatal Diagnosis and Prognosis*, (Lilford R. J., ed.) Butterworths, pp. 67-92.

Greene M. F., Haddow J. E., Palomaki G. E. & Knight G. J. (1988) Maternal serum alpha-fetoprotein levels in diabetic pregnancies. *Lancet* **ii**, 345-346.

Levitz M. & Selinger M. (1970) Plasma estriol levels in Class D diabetes of pregnancy. *Am J Obstet Gynecol* **105**, 82.

Masson G. N. & Sutherland H. W. (1973) Plasma oestriol in pregnancy complicated by diabetes mellitus. *J Obst Gynaecol Brit Comm* **80**, 536-541.

Milunsky A., Alpert E., Kitzmiller J. L., Younger M. D. & Neff R. K. (1982) Prenatal diagnosis of neural tube defects. VIII The importance of serum alpha-fetoprotein screening in diabetic pregnant women. *Am J Obstet Gynecol* **142**, 1030-1032.

Nachtigall L., Bassett M., Hogsander V. & Levitz M. (1968) Plasma estriol levels in normal and abnormal pregnancies: An index of fetal welfare. *Am J Obstet Gynecol* **101**, 638.

Reece E. A., Davis N., Mahoney M. J. & Baugarten A. (1987) Maternal serum alpha-fetoprotein in diabetic pregnancy: correlation with blood glucose control. *Lancet* **ii**, 275.

Selenkow H. A., Varma K., Younger D., White P. & Emerson K. (1971) Patterns of serum immunoreactive human placental lactogen (IR-HPL) and chorionic gonadotrophin (IR-hCG) in diabetic pregnancy. *Diabetes* **20**, 696-706.

Stewart M. O., Whittaker P. G., Persson B., Hanson U. & Lind T. (1989) A longitudinal study of circulating progesterone, oestradiol, hCG and hPL during pregnancy in type 1 diabetic mothers. *Br J Obstet Gynaecol* **96**, 415-423.

Taylor E. S., Hagerman D. D., Betz G , Williams K. L. & Grey P. A. (1970) Estriol concentrations in blood during pregnancy. *Am J Obstet Gynecol* **108**, 868.

Wald N. J., Cuckle H., Boreham J , Stirrat G. M. & Turnbull A. C. (1979) Maternal serum alpha-fetoprotein and diabetes mellitus. *Br J Obstet Gynaecol* **86**, 101-105.

Wald N. J., Cuckle H. S., Densem J. W., *et al.* (1988) Maternal serum screening for Down's syndrome in early pregnancy. *Br M J* **297**, 883-887.

Wald N. J., Cuckle H. S., Wu T. & George L. (1991) Maternal serum unconjugated oestriol and human chorionic gonadotrophin levels in twin pregnancies: Implications for screening for Down's syndrome. *Br J Obstet Gynaecol* **98**, 905-908.

Received 7 May 1991
Accepted 12 August 1991

British Journal of Obstetrics and Gynaecology
January 1992, Vol. 99, pp. 54–58

GYNAECOLOGY

Is Stage I epithelial ovarian cancer overtreated both surgically and systemically? Results of a five-year cancer registry review

CATHERINE B. FINN
Sheldon Research Fellow
D. M. LUESLEY
Senior Lecturer in Obstetrics & Gynaecology
E. J. BUXTON
Lecturer in Obstetrics & Gynaecology
Department of Obstetrics & Gynaecology, Dudley Road Hospital, Birmingham B18 7QH, UK
G. R. BLACKLEDGE
Reader in Medical Oncology
K. KELLY
Statistician
J. A. DUNN
Statistician
Cancer Research Campaign Clinical Trials Unit, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 3NE, UK
S. WILSON
Deputy Director
West Midlands Regional Cancer Registry, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 3NE

ABSTRACT

Objective To review the incidence of Stage I epithelial ovarian carcinoma in the West Midlands region and to identify prognostic factors that have a significant effect on survival.
Design A retrospective review of all Stage I ovarian cancer patients registered from 1.1.80 to 31.12.84.
Setting West Midlands Regional Cancer Registry.
Population 457 patients with Stage I ovarian cancer—373 with epithelial ovarian carcinoma.
Main outcome measures Survival at censor date of 30.6.89.
Results 28% developed recurrent disease, and the overall 5-year survival of the group was 70%. Univariate analysis of all possible prognostic factors showed that stage, adjuvant chemotherapy, histological grade and type, surgical rupture of the tumour, intact capsule histologically, clinical finding of ascites and the performance of peritoneal washings were significantly associated with survival. Adequate surgical staging as defined by FIGO was not significantly associated with survival. A multivariate analysis based on the Cox proportional hazard model identified histological grade, adjuvant chemotherapy, patient age and peritoneal washings as having independent prognostic effects. Surprisingly adjuvant chemotherapy and peritoneal washings had negative effects on survival.
Conclusions Although a retrospective review has limitations, it would appear that adequate surgical staging and adjuvant chemotherapy confer no benefit in terms of survival in Stage I disease.

Stage I epithelial ovarian cancer (EOC) is theoretically curable by surgery alone, yet the majority of patients have been treated with either post-operative radiotherapy or cytotoxic agents over the last two decades. The value of such treatment is not clear as neither management has been assessed in an appropriate fashion. Despite these efforts the relapse rate at 5 years remains between 20 and 30% (Aure *et al.* 1971a; Fisher & Young 1977; Webb *et al.* 1973). Hreshchyshyn (1980) has suggested that adjuvant therapy may be beneficial in selected patients, whilst Smith *et al.* (1975) in a small study where chemotherapy was given in a random fashion was unable to demonstrate any advantage in the treated patients. Wiltshaw (1987) reported morbidity from post-operative therapy to be approximately 10% and, from the same study, she reported that patients treated after primary laparotomy had the same relapse rate as non-treated patients at 2 years (20%). It would appear that there is a certain subgroup of patients with Stage I EOC who have an adverse prognosis from the outset and identification of this group may be beneficial in planning further management after primary laparotomy. We have reviewed the incidence of Stage I EOC in the West Midlands region. The primary objective was to identify factors that have a significant effect on survival and to determine the independent effect of these factors, with a view to identifying a group of high risk patients who may benefit from adjuvant treatment.

Subjects and methods

A retrospective analysis of all patients with ovarian cancer registered at the West Midlands Regional Cancer Registry from 1 January 1980 to 31 December 1984 was undertaken. Completeness of ascertainment for all malignant tumours in the region has been estimated at 98% (Waterhouse *et al.* 1976). Overall 2395 patients with ovarian cancer were registered during the study period. Exclusions comprised of cases treated in the region but with a usual place of residence outside the

Correspondence: Dr C. Finn, Birmingham Maternity Hospital, Edgbaston, Birmingham B15 2TG, UK.

region and death certificate only registrations (i.e. cases where no evidence of the malignancy could be obtained from the general practitioner or hospital to confirm details on the death certificate). All of the above records were examined and 457 records of Stage I ovarian cancer were identified. Demographic data and details of all possible prognostic factors were recorded. Details regarding duration of symptoms before presentation, presentation symptoms which included bleeding, pain and abdominal distension, presentation findings including the presence of ascites and pelvic or abdominal mass on clinical examination and radiological investigations were recorded. Rigourous details regarding the extent of surgery performed were noted which included whether the tumour was ruptured inadvertently or otherwise before its removal from the abdomen (surgical rupture). Stage was recorded as defined by the FIGO classification of 1975 (Scully 1975) and its adequacy by adherence to FIGO recommendations which included retroperitoneal node biopsy (adequate staging). Details regarding whether the capsule of the tumour was intact on histological examination (intact capsule) as well as histological type and grade were also noted. The type of adjuvant therapy given, if any, was also recorded. Follow-up data in terms of date of recurrence, type of second surgery, type of further treatment, date of death and cause of death were also recorded.

Statistical methods

Data were abstracted from the records held at the West Midlands Cancer Registry and stored using a Digital™ Systime VAX 11/70 minicomputer at the West Midlands Cancer Research Campaign Clinical Trials Unit. The statistical analyses were performed using the BMDP statistical software (Dixon *et al.* 1985).

For the analysis of this report the duration of survival was the primary endpoint. Survival time was defined as the time from initial operation until the date of death. The survival of the live patients was censored at the 30 June 1989. Initial univariate analysis of potential prognostic variables was performed using Kaplan-Meier survival curves (Kaplan & Meier 1958) and the differences between groups tested using the log-rank test (Peto *et al.* 1977).

The independent prognostic effect of variables was assessed by performing a multivariate analysis based on the Cox proportional hazards model (Cox 1972). A stepwise procedure was adopted. The criterion for inclusion of a variable was $P>0{\cdot}05$ and for removing a variable was $P<0{\cdot}05$. For the Cox multiple regression, only cases with complete data for all variables are considered. The analysis was repeated using the variables entered in the final model. Thus the analysis was based on 356 cases. The proportionality assumptions of the method were tested graphically using stratified Cox regression analysis and looking at the log minus log survival function plots. The stability of the variables entered in the final model was examined by repeating the analysis excluding each factor in turn. This was performed to identify any inherent association in the data. The adjusted hazard ratios were calculated using the regression coefficient from the final model.

Results

Population characteristics

A total of 457 patients were identified as having Stage I ovarian carcinoma, 26 had a non-epithelial tumour and 58 had a borderline epithelial ovarian carcinoma, giving 373 with invasive epithelial ovarian carcinoma. For the purposes of this review only the patients with invasive disease were considered for further analysis. The median age was 58 yearr (range 19–83). The median parity was 1 (range 0–8). The median duration of symptoms before presentation was 2 months (range 1–36). Abdominal distension was the commonest presenting symptom (312 patients) and the commonest finding at presentation was a pelvic mass (365 patients). The population characteristics are shown in Table 1. The histological subtypes of this population differs from that of the more advanced group of ovarian carcinoma. Unlike the 3:1 ratio of serous to mucinous tumours found in advanced EOC there was almost an even distribution in this population. Adequate staging, as defined previously, was carried out in 111 patients (30%). A total of 227 patients (61%) had Stage Ia disease, 31 (8%) Stage Ib, and 112 (30%) Stage Ic disease. A total of 132 patients (35%) received adjuvant chemotherapy, predominantly in the form of alkylating agents apart from a small percentage who received a platinum-based therapy in 1984; 53 (14%) received adjuvant radiotherapy to the pelvis alone, 105 (28%) developed recurrent disease and the overall 5-year survival was 70% (Figure 1). For those patients alive at censor date, median follow-up was 81 months (range 54–113).

Univariate analysis

Initial univariate log rank analysis identified factors significantly associated with survival (Table 2). This analysis was based on 359 cases as 14 had missing survival data. Variables

Table 1. Population characteristics (n = 373)

Variable	*n*	(%)
Symptom		
Distension	312	(83)
Pain	219	(59)
Bleeding	75	(20)
Clinical finding		
Pelvic mass	365	(98)
Ascites	36	(9)
Histology		
Serous	167	(45)
Mucinous	125	(34)
Clear	34	(9)
Endometriod	28	(7)
Unspecified adeno	19	(5)
Differentiation		
Well	256	(69)
Moderate	27	(7)
Poor	40	(11)
Unknown	50	(13)
Stage*		
Ia	227	(61)
Ib	31	(8)
Ic	112	(30)
Deaths		
Cancer	112	(30)
Treatment	1	(0.02)
Unrelated	13	(3)

*Three cases with unknown stage.

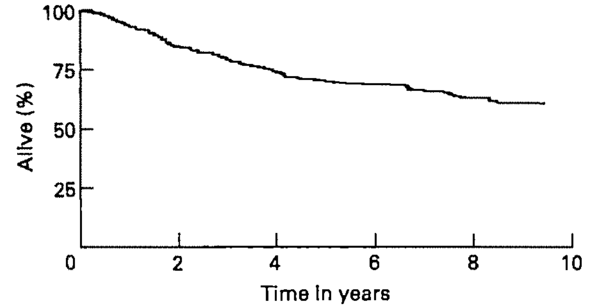


Fig. 1. Overall survival for 359 patients with Stage I epithelial ovarian cancer.

considered included patient age (using a cutpoint of 58), parity, duration of symptoms, presentation symptoms and findings, whether the capsule was intact on histological examination (intact capsule), histological type and grade, stage and its adequacy, details of surgery which included whether the tumour was ruptured before its removal from the abdomen (surgical rupture) and the use of adjuvant therapy. It was of interest to note that neither the adequacy of surgical staging ($P = 0{\cdot}57$) nor the use of adjuvant radiotherapy ($P = 0{\cdot}24$) were significantly associated with survival.

Multivariate analysis

To determine the independent prognostic effect of each of the factors and to exclude the possibility that the most highly significant variables might be masking the effect of other potentially significant factors, Cox regression analysis was performed using all variables considered in the univariate analysis. The assumptions implicit in the Cox model were satisfied. Table 3 tabulates the results of the final model from the stepwise analysis identifying histological grade, adjuvant chemotherapy, patient age and peritoneal washings as independent variables.

Discussion

Approximately 25% of patients with epithelial ovarian cancer present with disease confined to the ovaries. As 70% of these patients are cured by surgery alone, they are not always referred to an oncological unit. This review was therefore undertaken through the West Midlands Regional Cancer Registry and reflects the overall incidence and management of Stage I disease within a region with a female population of 2·4 million. Unlike many previously reported reviews, this is a population-based study and therefore is truly representative of the overall incidence and management of the disease. A strength of this study compared to other smaller reports is that formal review of all cases of EOC registered during the study period was undertaken. Furthermore tumours of low malignant potential were excluded from the analysis as they are a well described entity that clearly display a different natural history and behaviour from invasive tumours. Their inclusion would add an overall bias towards a good prognosis for the group.

Although 70% of patients are cured with conventional therapy, those patients who are surgically curable and who do not need further adjuvant therapy have not been clearly defined. Furthermore the value of adjuvant treatment in terms of survival advantage remains to be demonstrated. This review set out to identify factors that significantly influence prognosis.

Table 2. Univariate analysis ($n = 359$)

Variable	Group	No. dead	% survival	DF	χ^2	P value	Survival improved in group
Histological grade	Well	66/249	73%	2	39·4	0·00001	Well
	Mod	8/26	69%				
	Poor	50/84	40%				
Adjuvant chemotherapy	Yes	60/127	52%	1	14·8	0·0001	No
	No	64/232	72%				
Histological type	Ser	73/190	62%	2	16·6	0·0002	Muc
	Muc	27/121	78%				
	Clear	24/48	50%				
Age	<50	22/109	80%	3	18·5	0·0003	Younger
	50–60	45/98	54%				
	60–70	37/95	61%				
	70+	20/57	65%				
Stage	Ia	61/223	73%	2	15·2	0·0004	Ia
	Ib	13/30	57%				
	Ic	50/106	53%				
Washings	Yes	46/100	54%	1	11·1	0·0009	No
	No	78/259	70%				
Intact capsule	Yes	76/261	71%	1	9·2	0·002	Yes
	No	41/90	54%				
	Uk	6					
Ascites	Yes	19/35	46%	1	7·7	0·005	No
	No	105/322	67%				
	Uk	2					
Surgical rupture	Yes	22/44	50%	1	6·3	0·012	No
	No	102/315	68%				

Table 3. Summary of the Cox regression analysis ($n = 356$)

Step no.	Variable	Group	Regression coefficient	χ^2 to remove	*P*-value	Ratio of risks	Favourable features
1	Histological grade	Well *v* mod *v* poor	0·4468	19·34	0·00001	2·45	Well
2	Adj chemotherapy	Yes *v* No	−0·4965	6·93	0·009	0·61	No
3	Age	Continuous	0·0211	8·66	0·003	1·52	Younger
4	Washings	Yes *v* no	−0·4908	6·25	0·013	0·61	No

Favourable features: Grade—Well, Chemotherapy—No, Age—40, Washings—No. Unfavourable features: Grade—Poor, Chemotherapy—Yes, Age—60, Washings—Yes.

Grade was the most important predictor of outcome in this study as demonstrated previously by Dembo *et al.* (1990). There was a large proportion of cases with well differentiated tumours and these consistently had a better outcome.

Adjuvant chemotherapy was the second most important predictor of outcome in that it had an independent negative effect on prognosis. The role of adjuvant chemotherapy in the management of Stage I disease is unclear (Guthrie 1984). Our review, although retrospective, is the first to demonstrate an adverse outcome following the use of adjuvant chemotherapy in this group of patients and certainly questions the advisability of its use for the management of Stage I epithelial ovarian carcinoma. It also raises the question as to why a proper randomized trial has not been undertaken to assess the role of chemotherapy in the management of all substages and grades of Stage I disease.

Much has been written regarding adequate staging and its impact on treatment selection (Dembo *et al.* 1990; Young 1987). Only 30% of patients in our series were considered to have had an adequate staging procedure performed as defined by FIGO recommendations (Scully 1975). Despite this adequacy of staging there appeared to be no significant difference in terms of survival, even after accounting for all other variables. Of interest was the independent adverse effect of peritoneal washings on survival. This finding questions the role of peritoneal washings as part of the staging procedure. The increased risk in our patients might either reflect dissemination of tumour cells within the peritoneal cavity by the lavage fluid or alternatively reflect an effect on host immunity. The former hypothesis is supported by the FIGO report of 1988 (Pettersson 1988) on 8082 patients with invasive tumours. The said report included patients treated between 1979–1981. The 1986 FIGO classification was applied retrospectively to this group and analysis was performed on grade, histological type, stage and age. It is far from clear how this information was obtained, however in the analysis; grade, substage c (which included positive ascites, surgical rupture and capsular penetration), age and histological type were significant prognostic factors for Stage I ovarian cancer. Allowing for differences in the variables analyzed, the results of our present review where rigorous examination of cases was performed, are similar.

What is the value of this review? We feel it addresses two important issues—the role of adjuvant chemotherapy and the usefulness of the present staging procedure. Adjuvant chemotherapy as given in this review conferred a negative prognostic effect on survival. We accept that the role of platinum-based therapy as we know it in 1991 was not tested in this review and unfortunately no long-term comparative studies in Stage I patients are yet available. Furthermore we appreciate that as a retrospective review which has not been controlled, its findings preclude generalizations as applied to the average patient with Stage I disease. However like Guthrie's review (1984) it questions the role of adjuvant chemotherapy in this setting. We would therefore advocate a 'no treatment arm' in any future prospective randomized trials addressing the issue of adjuvant therapy in Stage I patients in an endeavour to finally address the role of such treatments if any. The issue of Stage Ia and Ib patients with moderate to well differentiated tumours has been recently addressed by Young *et al.* (1990), although that trial was flawed by the inclusion of borderline tumours, few clinicians would now offer this type of patient any form of adjuvant therapy. We would suggest that such patients be excluded from future studies. However, we feel that the remaining subsets of patients must all be included if we are to achieve an answer to this problem.

Adequate staging, as defined by FIGO, did not appear to confer any survival advantage in our review. More importantly perhaps was the independent negative effect of peritoneal washings on survival which would question the role of the present staging procedure. Dembo (1990) advocated a simplification of Stage I substaging using only grade, dense adherence and large volume ascites as these were the only factors found to be predictive of relapse in his review. His conclusions were validated using a second data set. The biological behaviour of this disease when confined to the ovary would appear to be totally different from the more aggressive advanced disease. We would advocate a thorough inspection of the abdomen as advised by FIGO but would question the role of peritoneal washings and retroperitoneal node biopsy when the disease seems to be truly confined to the ovary. Removal of the bulk of the tumour would appear to be all that is required. Perhaps the questions to be asked when dealing with this stage of disease is whether the disease is macroscopically confined to the ovary and whether there is positive ascites present?

We conclude from our analysis that histological grade, adjuvant chemotherapy, patient age and peritoneal washings are independent prognostic factors in Stage I epithelial ovarian cancer. Furthermore of potentially greater clinical relevance is that it suggests that adjuvant chemotherapy and adequate surgical staging, as defined by FIGO, confer no benefit in Stage I ovarian cancer and may in fact be detrimental to outcome.

Acknowledgment

I would like to thank all the staff at the West Midlands Regional Cancer Registry without whose help and co-operation this review would not have been possible.

References

Aure J. C., Hoeg K. & Kolstad P. (1971a) Clinical and histologic studies of ovarian carcinoma. Long-term follow-up of 990 cases. *Obstet Gynecol* **37**, 1-9.

Cox D. R. (1972) Regression models and life tables. *J Royal Stat Soc A* **34**, 187-220.

Dembo A. J., Davy M. L. J., Stenwig A. E., *et al* (1990) Prognostic factors in patients with Stage I epithelial ovarian cancer. *Obstet Gynecol* **75**, 263-273.

Dixon W., Brown M., Engelman L., *et al* (1985) In BMDP *Statistical Software Manual*, 5th ed., University of California Press, Berkeley.

Fisher R. & Young R. (1977) Advances in the staging and treatment of ovarian cancer. *Cancer* **39**, 967-972.

Guthrie D., Davy M. L. J. & Philips P. R. (1984) A study of 656 patients with 'early' ovarian cancer. *Gynecol Oncol* **17**, 363-369

Hreshchyshyn M. M., Park R. C., Blessing J. A., *et al.* (1980) The role of adjuvant therapy in Stage I ovarian cancer. *Am J Obstet Gynecol* **138**, 139-145.

Kaplan E. L. & Meier P. (1958) Non-parametric estimation from incomplete observations. *J Am Stat Assoc* **53**, 457-462.

Peto R., Pike M. C., Armitage P., *et al* (1977) Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. *Brit J Cancer* **35**, 1-39.

Pettersson F. (1988) *Annual Report on the Results of Treatment in Gynecological Cancer* 20th Vol., FIGO, Stockholm.

Scully R. E. (1975) World Health Organization classification and nomenclature of ovarian cancer. *Nat Cancer Inst Monogr* **42**, 5.

Smith J. P., Rutledge F. N. & Declos L. (1975) Results of chemotherapy as an adjunct to surgery in patients with localized ovarian cancer. *Semin Oncol* **2**, 277-281.

Waterhouse J., Muir C., Carrea P. & Powell J. (1976) In *Cancer Incidence in Five Continents*, Vol. III, IARC Scientific Publications, Lyons, France.

Webb M.J., Decker D. G., Mussey E. & Williams T. J. (1973) Factors influencing survival in Stage I ovarian cancer. *Am J Obstet Gynecol* **116**, 222-226.

Wiltshaw E., Osborne J. & Gallagher C. (1987) Laparoscopic follow-up of early ovarian cancer. In *Ovarian Cancer—The Way Ahead*, (Sharp F. & Soutter W P., eds), Royal College of Obstetrician & Gynaecologists, London, pp 277-282.

Young R. C. (1987) Initial therapy for early ovarian carcinoma. *Cancer* **60**, 2042-2049.

Young R. C., Walton L. A., Ellenberg S. S., *et al.* (1990) Adjuvant therapy in Stage I and Stage II epithelial ovarian cancer. Results of two prospective randomized trials. *New Engl J Med* **322**, 1021-1027.

Received 28 March 1991
Accepted 12 August 1991

British Journal of Obstetrics and Gynaecology
January 1992, Vol. 99, pp. 59–62

GYNAECOLOGY

A randomized clinical trial on the benefit of adhesiolysis in patients with intraperitoneal adhesions and chronic pelvic pain

A. A. W. PETERS
G. C. M. TRIMBOS-KEMPER
C. ADMIRAAL
J. B. TRIMBOS

Department of Gynaecology,
Leiden University Medical Centre

J. HERMANS

Department of Medical Statistics,
University of Leiden, The Netherlands

ABSTRACT

Objective To see whether surgical adhesiolysis would improve pelvic pain in women with pelvic adhesions.
Design Randomized clinical trial comparing surgery (adhesiolysis) with no surgery with final analysis of results after 9–12 months.
Setting Department of Gynecology, Leiden University Medical Center, the Netherlands.
Subjects 48 women known by laparoscopy to have stage II–IV pelvic adhesions.
Interventions Midline laparotomy and surgical adhesiolysis.
Main outcome results Pelvic pain assessed by the McGill pain score, subjective pain assessment and disturbance of daily activities.
Results 24 women were randomly allocated to undergo surgical adhesiolysis and 24 to a control group who did not have surgery. After 9–12 months there were no significant differences between the two groups overall with regard to pelvic pain. A subgroup of women with severe, vascularized and dense adhesions involving bowel (stage IV) had significantly less pelvic pain after adhesiolysis for two of the three methods of assessment.
Conclusions Adhesiolysis for the treatment of pelvic pain is not indicated in women with light or moderate degree pelvic adhesions. It may be beneficial in those with severe adhesions involving the intestinal tract.

A woman with chronic or recurrent pelvic pain presents a continuing clinical challenge. A fruitless search for somatic disease often results in visits to many different consultants. Various diagnoses are popular such as: 'chronic cystitis', 'irritable bowel syndrome' or 'pelvic pain syndrome'. These diagnoses do not lead to a better understanding of the problem and do not result in a successful treatment in most of these women. Because the results of surgical or pharmaceutical treatment are poor, the psycho-social aspects of chronic pain have gained more attention lately (Pearce *et al.* 1982).

A change in clinical attitude to the aetiology and management of a puzzling syndrome may result in useful therapeutic procedures being abandoned. Surgical adhesiolysis could be such a treatment.

Intraperitoneal adhesions are mainly caused by surgery and to a lesser extent by diseases such as endometriosis (Ellis 1982) and by pelvic infections (Weström 1980). After appendectomy, gynaecological operations are the second main cause of intraperitoneal adhesions in women (Raf 1969). This is the more important since the value of many of these gynaecological operations, such as correction of the retroverted uterus and ovarian wedge resection in women with polycystic ovarian disease (PCO), have been criticized lately.

From the surgical point of view adhesions cannot always be regarded as evil; most are symptom free and, in many instances, may well have had a protective effect. They may be life saving by preventing leakage from suture lines or by sealing-off inflammatory collections (Ellis 1982).

Nevertheless, gynaecologists are confronted with unwanted sequelae of adhesion formation. Infertility and ectopic pregnancy can be the adverse results of pelvic adhesions and much research has been devoted to the prevention and management of adhesions. Data about the relation between chronic pelvic pain and adhesions are conflicting. Some laparoscopic studies show a high frequency of adhesions in women with chronic pelvic pain and stress the importance of laparoscopy in the management of pelvic pain (Kresh *et al.* 1984). Others could demonstrate no difference in the occurrence of adhesions in women with chronic pelvic pain compared with those who had had laparoscopy for other reasons, such as sterilization and infertility (Cunanan *et al* 1983).

Controlled studies on the value of adhesiolysis are lacking. One of the problems is the measurement of the pain and the staging of the adhesions. Most staging systems for adhesions involving the pelvic organs have been developed by fertility surgeons and have been related to the prospect of pregnancy (Siegler 1977). The objective of the present study was to provide information on the significance of adhesions in relation to pelvic pain.

Correspondence: A. A. W. Peters, MD, PhD., Department of Gynaecology, Leiden University Medical Centre, PO Box 9600, 2300 RC Leiden, The Netherlands.

Table 1. Characteristics of the women randomized to active treatment by surgical adhesiolysis or an expectant wait-and-see policy (control group)

	Adhesiolysis (*n* = 24)	Control group (*n* = 24)
Age (years)		
Mean (range)	35·5 (21–58)	35·7 (23–56)
Parity		
Mean (range)	1·6 (0–4)	1·5 (0–5)
Nulliparous	5	4
Duration of pain (months)		
Median (range)	42 (6–350)	36 (8–240)
Severity of the adhesions		
Stage II (*n*)	4	6
Stage III (*n*)	11	12
Stage IV (*n*)	9	6
McGill pain score		
Median (range)	31 (20–35)	32·5 (18–40)
Daily activities disturbed (*n*)	18	20

n = no. of women.

The study was approved by the medical ethic board of the institution.

Patients and methods

Women with chronic pain referred to the department of gynaecology of the Leiden University Medical Centre were considered for entry in the study. The women had to have had pelvic pain for at least 6 months and had to have mastered the Dutch language sufficiently to understand the meaning of the study and to be able to cope with the pain questionnaire.

The following exclusion criteria were used: previous malignant disease; medical treatment for pelvic pain at the first visit to our clinic; mental retardation; psychiatric or psycho-therapeutic treatment during the two years preceding the study; suspicion of malignant disease at pelvic examination; abnormal findings at pelvic examination suggestive of pathology that could be the cause of the pain and prompt medical or surgical intervention.

The women who fulfilled the criteria for entry had a diagnostic laparoscopy. Intra-abdominal adhesions were staged as follows (modified from Kapur *et al* 1967).

Stage I: some filmy adhesions, not vascularized. Easy to release during laparoscopy.

Stage II: extensive, non-vascularized, filmy adhesions involving one or more intra-abdominal organs (uterus, adnexa, small bowel, colon, bladder) or the mesentery, mesocolon or omentum

Stage III: numerous, partly vascularized adhesions involving one or more intraperitoneal organs, possibly leading to impairment of the function of these organs

Stage IV: as for III but with dense vascularized adhesions involving the serosa of the small bowel or colon fixed to the outer peritoneum.

Pain was assessed by three different methods:

1. The Dutch version of the McGill pain questionnaire by a card sort method (Reading 1979). This questionnaire appears to be the most suitable for investigating the multidimensional character of chronic pelvic pain. It takes into consideration the sensory, emotional, practical and temporal aspects of pain. It results in a score ranging from 10 for minimal to 40 for maximal pain. An intra-individual change of the McGill score (delta McGill score) of 5 points was considered to indicate a clinically significant difference in the occurrence of pain. There had been no experience with the Dutch version of the MPQ card sort method before this study. If a SD of 5 points was assumed for the distribution of the delta-scores, a sample size of 21 in each group was sufficient to detect a difference of 5 points in mean delta-score (alpha = 0·05, power = 0·90).
2. A comprehensive pain history with attention to the interference of the pain with the daily activities.
3. A subjective pain score comparing the situation before and after treatment: pain improved, unchanged or worsened.

Pain was assessed using these methods before the laparoscopy and 9 to 12 months later. After laparoscopy, women with stage II, III and IV adhesions were randomized by a closed envelope system to two groups. In the first group a wait and see policy was adopted. In the second group adhesiolysis was performed.

All surgery was done by two of the authors (A.A.W.P. and J.B.T.). Efforts were made to minimize tissue trauma and prevent postoperative adhesion formation (Neuwirth 1987). A lower midline incision was used routinely and this was sometimes extended above the umbilicus to allow adequate inspection of the intra-abdominal adhesions. The surgical technique employed in the adhesiolysis operations included bowel preparation, prophylactic antibiotics, meticulous haemostases, sharp dissection with 'cold' instruments, prevention of dehydration of peritoneal surfaces by flushing with normal saline, and the use of atraumatic forceps and clamps. No magnification was used and no dextrans were instilled into the abdominal cavity following surgery.

Table 2. Pain assessment 9–12 months after laparoscopy in 24 women treated by adhesiolysis and in 24 women allocated to a wait-and-see policy (control group)

Pain assessment	Adhesiolysis group (*n* = 24)	Control group (*n* = 24)
Mean interval between randomization and assessment (months)	11·2	10·8
Delta McGill score* Mean (range)	−5·7 (−27 to +3)	−5·5 (−23 to +2)
No with a delta-score of ≥5 points	11	10
No. with subjective improvement	10	9
No. with less disturbance of daily activities	12	14

*Intra individual change of McGill score (McGill score before randomization minus McGill score at final assessment).

Table 3. No. of women with improvement in pelvic pain as assessed by the McGill pain score, subjective assessment and disturbance of daily activities, 9–12 months after laparoscopy in relation to the severity of adhesions

Severity of adhesions	Adhesiolysis group ($n = 24$)			Control group ($n = 24$)		
	McGill	Subjective	Disturbance	McGill	Subjective	Disturbance
Stage II	0/4	0/4	0/4	5/6	4/6	5/6
Stage III	3/11	2/11	4/11	4/12	4/12	6/12
Stage IV	8/9	8/9	8/9	1/6	1/6	3/6
Total	11/24	10/24	12/24	10/24	9/24	14/24

Results

Between 1982 and 1989 a total of 48 women with intraperitoneal adhesions, stage II or worse, was included in the study. Twenty four women were randomized to receive active treatment by surgical adhesiolysis and 24 were allocated to an expectant wait-and-see policy (control group). The two groups were comparable with respect to age, parity, duration of the complaints and stage of the adhesions, McGill pain score and the number in whom the pain caused disturbances of daily activities (Table 1). Twelve women in the adhesiolysis and 14 in control group had had previous laparotomies. All 48 women in the study were assessed again 9–12 months after the initial laparoscopy. There were no protocol violations or deviations. The second assessment was done by an investigator who was not aware of the group to which the women had been allocated.

There were no significant differences between the two groups at the second assessment (Table 2). Fig. 1 shows a scatterdiagram of the intra-individual changes in the McGill score in both groups before and after 'treatment'. An improvement of the pain occurred in both groups. The distribution of the McGill scores was similar for the two groups (Fig. 1).

Stratification according to the stage of adhesions revealed a beneficial effect of adhesiolysis in those with severe adhesions (stage IV) (Table 3). The difference between surgery and no treatment in women with severe intraperitoneal adhesions was statistically significant for two of the three methods of pain assessment (delta McGill score and subjective pain ($P<0{\cdot}01$, χ^2 with Yates' correction)). Women with stage II and III adhesions had no significant improvement in pelvic pain following surgical adhesiolysis (Table 3).

Discussion

There is a lack of prospective studies on the benefits of adhesiolysis in women with chronic pelvic pain. In prospective studies three criteria should be fulfilled. First, there should be random allocation to a treatment-free group and to minimize the placebo effect, surgical assessment should be postponed to more than 16 months after treatment as it has been shown that placebo effects are seldomly long lasting (Beecher 1961). Second, it is essential to stage the intraperitoneal adhesions to using a classification which includes other intraperitoneal structures as well as the pelvic reproductive organs. Third, the influence of the procedure on pelvic pain should be assessed by objective criteria. Several scoring systems have been constructed and are used in clinical practice. In our view the McGill pain-questionnaire meets most requirements (Reading 1979) but in addition the influence of the pain on the daily activity should also be assessed.

One of the problems of this kind of prospective randomized trial is that the recruitment of a large number of patients is virtually impossible. This was true for the present study. Consequently definite conclusions and recommendations are unjustified.

Doubt has been expressed as to whether adhesions cause pelvic pain (Cunanan *et al.* 1983). The present study confirms these doubts. In general, adhesiolysis was of no more benefit than a wait-and-see policy. Only those women with severe multiple vascularized adhesions involving the serosa of the small bowel or, to a lesser extent, the colon benefited from surgical adhesiolysis. The previous history can be helpful in selecting these women. They tended to have periods of exacerbation of the pain with the symptoms and physical findings of small bowel obstruction (sub-)ileus. These symptoms are often of a transient nature. Radiographic examination of the small bowel may confirm the existence of such adhesions. When performing adhesiolysis it is essential to take all precau-

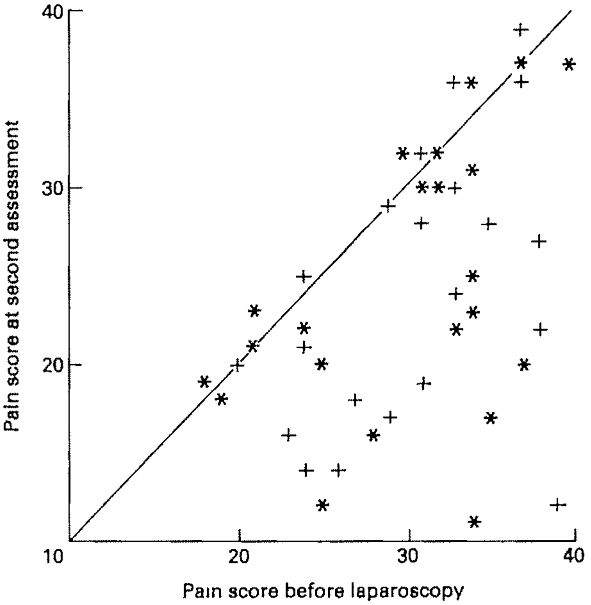


Fig. 1. Results of the McGill pain questionnaire score before and 9–12 months after active treatment by adhesiolysis in 24 women (+) or no treatment in 24 women (*).

tions before, during and after the operation to minimize the recurrence of adhesions. Our study suggests that adhesiolysis can be worthwhile in women with severe adhesions. Even in this category of patients psychosocial factors can be involved in the perception of the pelvic pain. These must be taken into consideration when management is planned to minimize the risk of performing after 'useless' operation in another long list of previous surgery.

References

Beecher H. K. (1961) Surgery as placebo. *JAMA* **176,** 1102–1107.

Cunanan R. G Jr., Courey N. G & Lipped J. (1983) Laparoscopic findings in patients with pelvic pain. *Am J Obstet Gynecol* **146,** 589–591.

Ellis H. (1982) The causes and prevention of intestinal adhesions. *Br J Surg* **69,** 241–243.

Kapur B. M. L., Rai P. C. & Gulati S. M. (1967) Prevention of experimental peritoneal adhesions by low molecular dextran. *Int Surg* **48,** 264–269.

Kresh A. J., Seifer D. B., Sachs C. B. & Barresa I. (1984) Laparoscopy in 100 women with chronic pelvic pain. *Obstet Gynecol* **64,** 672–674.

Neuwirth R S. (1987) Clinical aspects of the prevention and induction of adhesions in gynaecology. In *Reproductive Surgery* (DeCherney A. H. & Polan M. L. eds), Year Book Medical Publshers, Inc., Chicago, pp. 91–95.

Pearce S., Knight C. & Beard R. W. (1982) Pelvic pain—a common gynaecologic problem. *J Psychosom Obstet Gynecol* **1,** 12–17

Raf L. E. (1969) Causes of small intestinal obstruction. A study covering the Stockholm area. *Acta Chir Scand* **135,** 63–72.

Reading A. E. (1979) The internal structure of the McGill pain questionnaire in dysmenorrhoea patients. *Pain* **7,** 353–358.

Scott J & Huskinson E. C. (1976) Graphic representation of pain. *Pain* **2,** 175–184.

Siegler A. (1977) Surgical treatments for tubo-peritoneal causes of infertility since 1967. *Fertil Steril* **28,** 1019–1032.

Westrom L (1980) Incidence, prevalence and trends of acute pelvic inflammatory disease and its consequences in industrialised countries. *Am J Obstet Gynecol* **138,** 880–892.

Received 28 January 1991
Accepted 24 September 1991

British Journal of Obstetrics and Gynaecology
January 1992, Vol. 99, pp. 63–66

GYNAECOLOGY

Diagnosis of bacterial vaginosis in a gynaecology clinic

P. E. HAY
Honorary Senior Registrar

D. TAYLOR-ROBINSON
Professor of Genitourinary Medicine and Microbiology

Division of Sexually Transmitted
Diseases, Clinical Research Centre,
Harrow, Middlesex
The Jefferiss Wing,
St Mary's Hospital,
London W2 1NY

R. F. LAMONT
Consultant in Obstetrics and Gynaecology

Department of Obstetrics and
Gynaecology, Northwick Park
Hospital, Harrow

ABSTRACT

Objective To estimate the prevalence of bacterial vaginosis in women referred to a gynaecology clinic, and to compare two methods of diagnosing bacterial vaginosis.
Setting Gynaecology Clinic at Northwick Park Hospital
Subjects 114 women aged 16 to 65 referred consecutively to the gynaecology clinic of one consultant.
Main outcome measures Detection of bacterial vaginosis by standard compound criteria and by examination of a Gram stained smear of fluid from the posterior vaginal fornix.
Results Bacterial vaginosis was detected by both the Gram stain and the compound criteria in 13 women. There was no correlation between the symptom of vaginal discharge and the diagnosis of bacterial vaginosis in this population, but the presence of discharge noted by the clinician was associated with bacterial vaginosis.
Conclusions The prevalence of bacterial vaginosis was 11%. The Gram stain provides a simple and inexpensive method for laboratory confirmation of bacterial vaginosis where facilities for using the compound criteria are not available.

Bacterial vaginosis is the commonest cause of vaginal discharge occurring in women attending genitourinary medicine clinics in developed countries (Hillier & Holmes 1990). Patients often present with a malodorous vaginal discharge although many are asymptomatic. The diagnosis is established by detecting at least three of four compound criteria: a thin homogeneous vaginal discharge; a vaginal pH of >4·7; a characteristic 'amine' odour released when alkali (10% KOH wt/vol) is added to a specimen of vaginal fluid; and at least 20% of epithelial cells having the appearance of 'clue cells' in a wet mount of vaginal fluid (Eschenbach *et al.* 1988). Alternative laboratory-based tests include the use of Gram stain (Spiegel *et al.* 1983) or gas liquid chromatography (Krohn *et al.* 1989).

Bacterial vaginosis is a polymicrobial condition in which a decrease in vaginal acidity and in the concentration of lactobacilli is accompanied by an increase of a 100-fold or more in the concentration of other micro-organisms. No single micro-organism is detected in all women with bacterial vaginosis, but *Gardnerella vaginalis, Bacteroides* species, *Mycoplasma hominis* and *Mobiluncus spp.* have been associated with bacterial vaginosis in most studies. The triggers for the change in flora are currently unidentified, but might include hormonal factors and exogenous factors related to sexual intercourse or sexually transmitted infections (Sobel 1989).

Many physicians regard bacterial vaginosis as a harmless abnormality and do not recommend treatment in the absence of symptoms (Eschenbach *et al.* 1988). However, bacterial vaginosis and the organisms associated with it have been associated with preterm labour and delivery (Gravett *et al.* 1986a, b; Lamont *et al*; 1986; McDonald *et al.* 1991) and with postpartum maternal and neonatal infections (Berman *et al.* 1987; Hillier *et al.* 1988) and, therefore, may contribute to obstetric morbidity and mortality. Bacterial vaginosis has been strongly associated with the development of vaginal cuff infections following hysterectomy in two studies (Soper *et al.* 1990; Larsson *et al.* 1991). An association with pelvic inflammatory disease has also been postulated (Eschenbach *et al.* 1988; Paavonen *et al.* 1987). If these complications are confirmed it will become important that women with bacterial vaginosis, symptomatic or otherwise, are identified and treated actively.

The lowest reported prevalence of bacterial vaginosis is 5% found for women attending a student health centre in the USA for an annual examination (Hillier & Holmes 1990). In clinics for sexually transmitted diseases the reported prevalence has been between 24% and 37% (Eschenbach *et al.* 1988; Hallen *et al.* 1987; Hill *et al.* 1983; Moi 1990). While not regarded as a condition for which male partners require treatment, the epidemiology of the condition has some of the characteristics of a sexually transmitted disease (Sobel 1989; Amsel *et al.* 1983) and is associated with increasing age and the presence of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* (Hillier & Holmes 1990; Sobel 1989).

There is little information on the prevalence of bacterial vaginosis in the UK outside genitourinary medicine clinics. The population served by Northwick Park Hospital consists predominantly of non-manual workers with a large Asian community and the prevalence of sexually transmitted diseases is low. In an earlier study of women attending an antenatal clinic in this hospital, in which a sensitive technique (direct immunofluorescence; Syva, MicroTrak) was used, the prevalence of cervical infection with *C. trachomatis* was 0·6% (PM Furr,

Correspondence: Dr P E. Hay, Honorary Senior Registrar, The Jefferiss Wing, St Mary's Hospital, Norfolk Place, London W2 1NY.

Table 1. Presenting problem of 114 women attending a gynaecology outpatient clinic in relation to the presence of bacterial vaginosis (BV)

Indication for referral	Total no. of women	Women with BV *n*	(%)
Sterilization request	12	2	(17)
Menstrual problems	36	3	(8)
Infertility	8	3	(37)
Pelvic pain or dyspareunia	11	0	(0)
Abnormal cervical cytology	11	2	(18)
Vaginal discharge	3	1	(33)
Incontinence	6	0	(0)
Other	27	2	(7)
Total	114	13	(11)

Clinical Research Centre, Harrow, personal communication). It follows that a low prevalence of bacterial vaginosis might be anticipated in this population if the condition is associated with sexually transmitted infections. We undertook, therefore, a survey in the gynaecology clinic to assess the prevalence of bacterial vaginosis in this population and to assess the validity of screening for it using the Gram stain.

Subjects and methods

Consecutive new clinic attenders, 15–65 years of age, who required vaginal examination were eligible for enrolment. Verbal consent to the collection of specimens was sought. Patients were then requested to complete a short confidential questionnaire.

After passage of a vaginal speculum the presence or absence of vaginal discharge was noted. A sample of posterior fornix vaginal fluid was obtained using a 10 µl bacteriology loop. This was smeared on a glass slide and fixed with acetone. The slides were stained by Gram's method and stored for reading in one batch at the end of enrolment. The microscopist (P.E.H.) was unaware of the other results and used the criteria of Spiegel *et al.* (1983) to diagnose bacterial vaginosis. In this method the numbers of organisms per high power field (× 1000) are graded as: 1+, <1 per field; 2+, 1–5 per field; 3+, 5–30 per field; 4+, >30 per field. Large Gram-positive bacilli are assumed to be *Lactobacillus* morphotypes and smaller Gram-variable coccobacilli to be *Gardnerella* morphotypes. A second vaginal sample was taken to measure pH and was then placed on a slide for the addition of 10% KOH to detect an amine odour. This slide was examined subsequently with dark-field microscopy for the presence of fungal hyphae. The pH was measured using paper (Whatman International, Maidstone, UK) with a scale graded from 3·0 to 7·0 in units of 0·5. A third sample was mixed with a drop of normal saline and examined immediately for the presence of clue cells, *Trichomonas vaginalis* and *Candida* spp. using dark field microscopy. The diagnosis was discussed with those women diagnosed as having bacterial vaginosis by the compound criteria, and, if requested, they were treated with metronidazole.

Statistical analysis

The χ^2-test was used for analysing proportional data. Student's *t*-test was used for comparison of means for normally distributed data.

Results

Study population

One of 119 eligible patients declined to take part in the study. A further four patients were excluded because of heavy menstrual flow. Indications for referral to the clinic are shown in Table 1. The mean age of the 114 women enrolled was 36·2 years (range 16–65 years). One of 14 post-menopausal women (mean age 54·8 years) was diagnosed as having bacterial vaginosis as were 12 of 100 premenopausal women (mean age 33·6 years). Of the 114 women, 89 were of Caucasian origin, 17 were from the Indian sub-continent and 8 were Afro-Caribbean.

There was no statistically significant association between the presence of bacterial vaginosis and the following factors reported on the patient questionnaires: smoking history (35/114); contraceptive use (oral contraception 20, condom 20, other 10, none 64); time since menstruation (median 15·0 days); parity (mean 2·06, nulliparous 30); history of abortion (9/114) or miscarriage (25/114); occurrence of intercourse within the last month (83/114); number of lifetime partners (mean 2·12); age at first intercourse (mean 20·0 years); previous treatment for thrush (42), other genital infection (*T. vaginalis* 4, gonorrhoea 3, chlamydial infection 3, bacterial vaginosis 2) or pelvic infection (7). In response to the questionnaire, 21 patients reported a vaginal discharge; of these, only two had bacterial vaginosis and in two *Candida* spp. were detected on microscopy.

Diagnostic tests

The number of patients positive by each criterion is shown in Table 2. Thirteen women were diagnosed as having bacterial vaginosis by the compound criteria and the same 13, but none of the others, was positive by the Gram stain criteria. All those diagnosed as having bacterial vaginosis had a vaginal pH of >4·5 (range 5·0–6·5). The mean pH value for these women was 5·73 (95% CI 5·42–6·03) compared to a value of 4·42 (95% CI 4·27–4·58) for the 101 women without bacterial vaginosis ($P<0{\cdot}002$). Twenty-three other women had a pH

Table 2. Prevalence of individual criteria for the diagnosis of bacterial vaginosis (BV) in 114 women attending a gynaecology outpatient clinic

Diagnostic criteria	Women with BV (*n*=13)	Women without BV (*n*=101)
Compound criteria		
pH >4·5	13	23
Clue cells >20%	13	0
Amine test positive	11	1
Vaginal discharge	11	33
Gram stain	13	0

*Bacterial vaginosis defined as the presence of at least three of the four compound criteria.

value of >4·5. Possible factors contributing to a high pH were identified in 21 of these women: eight were post-menopausal, eight had blood-stained discharges, two had cervicitis with excess cervical mucus in the vagina, as was the case for one woman with a cervical polyp, one patient had a recto-vaginal fistula, and sperm were seen in the fluid of one woman. The remaining two women had a vaginal pH value of 5·0. Similar factors were present in two of the 13 women with bacterial vaginosis; one was post-menopausal and one had a blood-stained discharge.

Two women had between 1% and 20% clue cells detected but were not diagnosed as having bacterial vaginosis. There was a positive amine test on the sample containing sperm, as well as a raised pH, but there were no clue cells and no discharge was detected. There were only two patients for whom the result of the Gram stain was neither obviously normal (4+ *Lactobacillus* morpho-types and 0 to 2+ other morphotypes) or abnormal (4+ *Gardnerella* morphotypes and 0 to 2+ *Lactobacillus* morphotypes). One post-menopausal woman with a cystocoele had 4+ Gram negative rods but also 4+ *Lactobacillus* morphotypes, the latter excluding the diagnosis of bacterial vaginosis on the Spiegel criteria. One other woman had a mixed flora containing 3+ *Gardnerella* and 3+ *Lactobacillus* morphotypes. The dark-field examination of vaginal fluid from this woman was reported as showing 5% clue cells.

Candida spp. were detected in two women on dark-field examination, and *T. vaginalis* in association with bacterial vaginosis in one woman.

Discussion

The overall prevalence of bacterial vaginosis in this clinic population was 11%, which is in the lower part of the range reported previously from other centres. This is likely to be related to the low prevalence of sexually transmitted diseases in this population and also the small number of patients attending for treatment of a vaginal discharge. In contrast to patients attending clinics of genitourinary medicine, detection of bacterial vaginosis did not predict the symptom of vaginal discharge, although it did correlate with the clinician's assessment of abnormal discharge. A study of this size lacks the statistical power to demonstrate subtle epidemiological associations of bacterial vaginosis. Thus, although women referred for investigation of infertility had the greatest prevalence of bacterial vaginosis (3/8), the number is too small to demonstrate a significant association and a larger study of this group of patients might be warranted.

Bacterial vaginosis is generally considered to be a condition of premenopausal women. Nevertheless, the woman in whom both trichomoniasis and bacterial vaginosis were diagnosed was three years post-menopausal. In this regard it is noteworthy that large numbers of lactobacilli remain in the vagina and the vaginal pH remains acidic for approximately 5 years after the menopause (Redondo-Lopez *et al.* 1990), so that an increase in pH can still be predictive of bacterial vaginosis. However, among the individual criteria used to diagnose bacterial vaginosis, a raised pH is recognised as the most sensitive but least specific. False positive amine tests occur rarely but have been reported when semen is present (Eschenbach *et al.* 1988). The Gram stain was strikingly abnormal in patients with bacterial vaginosis, diagnostic confusion arising rarely. It was 100% specific and sensitive in comparison with the compound criteria for the diagnosis of bacterial vaginosis. Spiegel *et al.* (1983) were of the same opinion based on observations on 25 women with bacterial vaginosis in a study group of 60. However, in a larger study of bacterial vaginosis in pregnant women (Krohn *et al.* 1989), the Gram stain was reported to have a specificity of 95% but a sensitivity of only 62%. These investigators commented that there were several different microscopists involved so that inter-observer errors in establishing the diagnosis of bacterial vaginosis were possible.

Confusion may arise in making the diagnosis because it is apparent that at times there must be an intermediate condition comprising a mixed flora, in which lactobacilli are present but not dominant, together with increased numbers of bacterial vaginosis-associated organisms. This state may be represented by those patients in whom between 1% and 20% clue cells are seen. Inclusion of such women in a longitudinal study might allow identification of women in whom bacterial vaginosis is developing or regressing spontaneously and assist in the elucidation of the mechanisms that trigger the onset or disappearance of bacterial vaginosis. It is likely that the power of longitudinal studies to examine epidemiologic associations of bacterial vaginosis would be increased by inclusion of patients who might have abnormal flora but who would not otherwise have bacterial vaginosis diagnosed on the basis of the compound criteria. Although the compound criteria are adequate for clinical diagnosis, the subjective element involved in their detection makes them imprecise for epidemiological studies in that they define a somewhat arbitrary cut-off in a continuum from normal to abnormal flora.

If the associations of bacterial vaginosis with complications of pregnancy and pelvic inflammatory disease are confirmed, it would be important for physicians outside specialist clinics to be able to make the diagnosis of bacterial vaginosis simply and reliably. Not many are likely to have access to microscopes or the training and time to perform dark-field examinations of vaginal fluid to look for clue cells. However, it is simple to determine the vaginal pH, a test which is highly sensitive for the detection of bacterial vaginosis, but of relatively low specificity. We concur with the finding (Thomason *et al.* 1990) that in the absence of a microscope, the amine test provides a specific and relatively sensitive method for confirming the diagnosis. The diagnostic precision would be improved by confirming that unprotected intercourse has not occurred in the preceding 24 h. If laboratory confirmation were required, a smear of vaginal fluid for Gram staining by a microbiologist could be made using equipment and transport services already available for performing cervical cytology. This would be superior to requesting culture of a high vaginal swab. This approach to the diagnosis of bacterial vaginosis would allow rapid treatment. However, it is important that potentially more serious conditions which often co-exist with bacterial vaginosis, such as infection with *N. gonorrhoeae, C. trachomatis* or *T. vaginalis* are not missed, and screening for these infections in women and their partners should be considered when diagnosing bacterial vaginosis.

References

Amsel R., Totten P A., Spiegel C A., Chen K. C. S., Eschenbach D. A. & Holmes K. K. (1983) Nonspecific vaginitis: diagnostic criteria and microbial and epidemiologic associations. *Am J Med* **74,** 14-22.

Berman S M., Harrison H. R., Boyce W. T., Haffner W. J. J., Lewis M. & Arthur J. B. (1987) Low birth weight, prematurity, and post-partum endometritis association with prenatal cervical *Mycoplasma hominis* and *Chlamydia trachomatis* infections. *JAMA* **257,** 1189-1194.

Eschenbach D. A., Hillier S. H., Critchlow C., Stevens C., DeRouen T. & Holmes K. K. (1988) Diagnosis and clinical manifestations of bacterial vaginosis. *Am J Obstet Gynecol* **158,** 819-828.

Gravett M. G., Hummel D., Eschenbach D. A. & Holmes K. K. (1986a) Preterm labor associated with subclinical amniotic fluid infection and with bacterial vaginosis. *Obstet Gynecol* **67,** 229-237.

Gravett M G., Nelson H.P., DeRouen T., Critchlow C., Eschenbach D. & Holmes K. K. (1986b) Independent associations of bacterial vaginosis and *Chlamydia trachomatis* infection with adverse pregnancy outcome. *JAMA* **256,** 1899-1903.

Hallen A., Pahlson C & Forsum U. (1987) Bacterial vaginosis in women attending a STD clinic: diagnostic criteria and prevalence of *Mobiluncus* spp. *Genitourin Med* **63,** 386-389.

Hill L. H., Ruparella H. & Embil J. A. (1983) Nonspecific vaginitis and other genital infections in three clinic populations. *Sex Transm Dis* **10,** 114-118.

Hillier S. & Holmes K. K. (1990) Bacterial vaginosis. In *Sexually Transmitted Diseases*, 2nd edn., (Holmes K. K., Mårdh P. A., Sparks P. F. & Wiener P. J., (eds), McGraw-Hill, New York, p 547-559.

Hillier S. L., Martius J., Krohn M., Kiviat N., Holmes K. K. & Eschenbach D. A. (1988) A case-control study of chorioamnionic infection and histologic chorioamnionitis in prematurity. *New Engl J Med* **319,** 972-977.

Krohn M. A., Hillier S. L. & Eschenbach D. A. (1989) Comparison of methods for diagnosing bacterial vaginosis among pregnant women. *J Clin Microbiol* **27,** 1266-1271.

Lamont R. F., Taylor-Robinson D., Newman M., Wigglesworth J. & Elder M. G. (1986) Spontaneous early preterm labour associated with abnormal genital bacterial colonisation. *Br J Obstet Gynaecol* **93,** 4-10.

Larsson P-G, Platz-Christensen J-J, Fursum U. & Pahlson C. (1991) Clue cells in predicting infections after abdominal hysterectomy *Obstet Gynecol* **77,** 450-452.

McDonald H. M., O.Loughlin J. A., Jolley P, Vigneswaren R. & McDonald P. J (1991) Vaginal infection and preterm labour. *Br J Obstet Gynaecol* **98,** 427-435.

Moi H. (1990) Prevalence of bacterial vaginosis and its association with genital infections, inflammation, and contraceptive methods in women attending sexually transmitted and primary health clinics *Int J STD AIDS* **1,** 86-94.

Paavonen J., Teisala K., Heinonen P. K., *et al.* (1987) Microbiological and histopathological findings in acute pelvic inflammatory disease. *Bi J Obstet Gynaecol* **94,** 454-460.

Redondo-Lopez V., Cook R. L. & Sobel J. D. (1990) Emerging role of lactobacilli in the control and maintenance of the vaginal bacterial microflora. *Rev Infect Dis* **12,** 856-872.

Sobel J. D. (1989) Bacterial vaginosis—An ecologic mystery *Ann Intern Med* **111,** 551-553.

Soper D. E., Bump R. C. & Hurt W. G. (1990) Bacterial vaginosis and trichomoniasis vaginitis are risk factors for cuff cellulitis after abdominal hysterectomy. *Am J Obstet Gynecol* **163,** 1016-1023.

Spiegel C. A., Amsterdam R. & Holmes K. K. (1983) Diagnosis of bacterial vaginosis by direct Gram stain of vaginal fluid. *J Clin Microbiol* **18,** 170-177.

Thomason J. L., Gelbart S. M , Anderson R. J., Walt A. K., Osypowski P. J. & Broekhuizen F. F. (1990) Statistical evaluation of diagnostic criteria for bacterial vaginosis. *Am J Obstet Gynecol* **162,** 155-160.

Received 28 June 1991
Accepted 25 September 1991

British Journal of Obstetrics and Gynaecology
January 1992, Vol 99, pp. 67–74

REPRODUCTIVE SCIENCE

Intergenerational studies of human birthweight from the 1958 birth cohort.
1. Evidence for a multigenerational effect

IRVIN EMANUEL
Professor

Department of Epidemiology and Pediatrics, Maternal and Child Health Program, Child Development and Mental Retardation Center, University of Washington

*HAROULLA FILAKTI
EVA ALBERMAN
Professor

STEPHEN J. W. EVANS
Professor

Department of Clinical Epidemiology, London Hospital Medical College, London, UK

ABSTRACT

Objective To investigate possible multigenerational influences on birthweight.

Design Data from the longitudinal study of one week's births in 1958 up to the age of 23 years, the British National Child Development Study, were utilized. These provide socio-biological information on the parents of the cohort, on the cohort members from birth onwards, and on the pregnancies and the birthweight of any babies born to the cohort members.

Main outcome measure The main outcome was the birthweight of babies born to the cohort members, for whom complete intergenerational data were available for 1638 firstborn. Multiple regression modelling was used to investigate any associations between their birthweight and characteristics of their parents and grandparents.

Results Significant positive associations were found between babies' birthweight and parental birthweight but not gestational age. For the babies born to female cohort members additional findings included associations between their birthweight and the height of the maternal grandmother and the social class of the maternal grandfather, even after adjustment for such strong predictors of birthweight as maternal weight, smoking habit in pregnancy and baby's sex and birth order.

Conclusion These results thus offer support for a multigenerational influence on birthweight passed through the maternal line.

On the basis of a cohort analysis of mortality rates in the United Kingdom, Kermack *et al.* (1934) concluded that the health of infants depends on the health of mothers, and that health in later life is determined to a large extent by the state of health developed during childhood. With that background, Baird and his colleagues in Aberdeen studied reproductive outcomes as they may relate to the growth and the childhood environmental conditions of mothers. The study of simple measures, such as maternal stature and maternal social and marital mobility, led to the conclusion that pregnancy outcome is influenced both by conditions under which a mother was born and grew up, and by the conditions under which her pregnancy occurred (Baird 1947, 1962, 1985; Baird & Illsley 1952; Illsley 1955; Thomson 1959; Illsley & Mitchell 1984). Intergenerational factors have been defined as 'those factors, conditions, exposures and environments experienced by one generation that relate to the health, growth, and development of the next generation' (Emanuel 1986), and the outcomes for which these seem to be important are those for which the poor are at high risk compared to the well-off.

Since the early Scottish studies, the relation of maternal stature to infants' birthweight and/or gestational duration has been demonstrated in all populations studied, including European Caucasians, Blacks, Chinese, Malays, East Indians, and Central American Indians (Chen *et al.* 1963; Butler & Alberman 1969; Kapur *et al.* 1971; Singer *et al* 1973; Barron 1974; Lechtig *et al.* 1975; Toth *et al.* 1983). Further, maternal stature has been related to infant mortality, perinatal mortality and neural tube defects (Martorell *et al.* 1981; Anderson *et al.* 1958; Baird & Thomson 1969).

Moreover, a number of studies have confirmed the relation first reported by the Ounsteds (1968, 1973) between the mother's own birthweight and baby's birthweight and relative intrauterine growth (Hackman *et al.* 1983; Toth *et al.* 1983; Klebanoff *et al* 1984; Klebanoff & Yip 1987), and between mother's and baby's relative intrauterine growth (Klebanoff *et al.* 1989). One study found a relation between mother's birthweight and baby's neonatal morbidity (Hackman *et al.* 1983). Relations have also been found between mother's birthweight and adult height, prepregnancy weight, and pregnancy weight gain (Hackman *et al.* 1983; Langhoff-Roos 1987).

Recently, intergenerational factors in pregnancy outcome have been reviewed more completely (Emanuel 1986; Emanuel *et al.* 1989). The potential importance of fetal growth dis-

Correspondence: Professor Eva Alberman, Wolfson Institute of Preventive Medicine, Medical College of St Bartholomew's Hospital, Charterhouse Square, London EC1M 6BQ, UK.
*Now at The Office of Population Censuses and Surveys London, UK.

turbance to adult health, including reproductive health has been highlighted (Hytten 1990), and together, findings of various studies suggest that multigenerational influences may be operating through their effect on maternal growth in the determination of birth outcome. Preliminary data from Aberdeen also suggested the possibility of a three generation influence on birthweight (Baird 1985).

The study reported here is to investigate the extent of multigenerational influence in a national birth cohort of British births, the National Child Development Study (NCDS) (Shepherd 1985).

Subjects and methods

The births of the cohort members

The cohort began with the National Birthday Trust Fund Perinatal Mortality Survey (Butler & Bonham 1963; Butler & Alberman 1969), a study of all births in England, Wales and Scotland during the week of March 3–9, 1958. The sample consisted of 98% of all eligible births, and included 16 994 single births, 412 twins and 12 triplets. Birth data on this cohort were largely obtained from the midwives in charge of the deliveries who were asked to complete structured forms, partly by interview and partly from data derived from obstetric records where available. The data collected included gestational age in days, and birthweight of the cohort member in pounds and ounces; occupation of both parents; height (without shoes), non-pregnant weight, and smoking history of the mother. The original data on the non-pregnant weight of mothers of the cohort members were recorded in stones (14 pounds) and pounds, but was unfortunately coded into class intervals of stones; for use in analyses the midpoint of each interval was converted into kilograms.

The cohort was followed at 7, 11, 16 and 23 years. At last follow-up in 1981 at age 23 years there was a 72% response of those original cohort members, excluding those who had died or emigrated (Shepherd 1985).

Twenty-three year follow-up

In 1981 standardized interviews were administered to the cohort by trained interviewers. A large body of information was collected on their socioeconomic, educational and health status, and information was obtained on all liveborn children born to the cohort members up to that time. Of the 6129 singleton female Caucasian cohort members who were followed at 23 years, 2287 had reported having one or more births, although only 1957 gave complete data on the number of their children and their birth order. Of the 6133 singleton male Caucasian cohort members 1059 had reported fathering one or more births.

Most of the relevant data were not available for the mothers of the children of the male cohort members (their spouses or partners) nor for the fathers of the children of the female cohort members. Therefore only indirect comparisons can be made of the relative importance of the mother or father with regard to possible intergenerational effects.

The cohort members reported their own heights (in feet and inches) and weights (in pounds) (non-pregnant for females) at age 23 years. and the birthweights (but not gestational age) of their babies. In a previous report (Alberman *et al.* 1991) it was shown that the mean height of male cohort members who were followed to 23 years was 177·6 (SE 0·11) cm, slightly higher than the 176·0 (SE 0·3) cm in a national British sample aged 20–24 in 1980; and that of the female cohort members 162·5 (SE 0·11) cm compared with 161·5 (SE 0·25) cm for the national sample (Knight & Eldridge 1984) but otherwise their height distributions followed the national patterns for sex and social class. The cohort members who had children by the age of 23 years were on average of slightly lower social class than the sample as a whole.

Enquiries were made about the smoking habits of the cohort members, but unfortunately information about smoking in pregnancy was asked only in relation to the most recent birth to female cohort members. The effect of maternal smoking is of such importance that the main analyses for female cohort members were based only on those in which this information was available.

Variables used in the analyses and their classification

All measured data were converted to metric equivalents. Birthweight centiles for week of gestation had been categorized for

Table 1. Description of derived sample female cohort members—all most recent births

	Valid cases	Missing	Total
F2 Mother's smoking	1734	223	1957
F3 Baby's birth order	1731	3	1734
F3 Baby's birthweight (g)	1724	7	1731
F3 Baby's gender	1721	3	1724
F2 Mother's birthweight (g)	1610	111	1721
F2 Mother's gestation (days)	1408	202	1610
F2 Mother's non-pregnant weight (kg)	1382	26	1408
F2 Mother's adult height (cm)	1376	6	1382
F2 Father's social class	1000	376	1376
F1 Grandfather's social class	939	61	1000
F2 Mother's maternal age (years)	939	0	939
F1 Grandmother's height (cm)	899	40	939
F1 Grandmother's non-pregnant weight (kg)	887	12	899
F1 Grandmother's smoking	880	7	887
Total	880	1077	1957

Table 2. Description of predictor variables female cohort members—all most recent births

Sample size = 880	Mean	(SD)
Continuous variables		
F1 Grandmother's height (cm)	160·7	(6·6)
F1 Grandmother's non-pregnant weight (kg)	59·2	(9·6)
F2 Mother's birthweight (g)	3244·0	(507·0)
F2 Mother's gestation (days)	281·7	(12·6)
F2 Mother's adult height (cm)	160·9	(6·5)
F2 Mother's non-pregnant weight (kg)	58·4	(9·0)
F3 Baby's birthweight (g)	3276·0	(528·0)
F2 Mother's maternal age (years)	21·9	(1·4)
Categorical variables	*No*	*(%)*
F1 Grandfather's social class:		
Non-manual	143	(16)
Manual	737	(84)
F1 Grandmother's smoking·		
Non-smoking	433	(49)
Smoking	447	(51)
F2 Mother's smoking:		
Non smoker + given up by fourth month	513	(58)
Smoked from fifth month and over	367	(42)
F2 Father's social class:		
Non-manual	197	(22)
Manual	683	(78)
F2* Mother's birthweight centile:		
<10	94	(11)
10–24	126	(15)
25–50	246	(28)
51–75	191	(22)
76–90	133	(15)
>90	79	(9)
F3 Baby's gender:		
Male	445	(51)
Female	435	(49)
F3 Baby's birth order:		
1	539	(61)
2	290	(33)
3	45	(5)
4	6	(1)

*Based on sample size = 869.

Sample is restricted to F3 singleton livebirths with full information on predictor variables

the second report on this cohort (Butler & Alberman 1969) as follows: <10th, 10th–24th, 25th–50th, 51st–75th, 76–90th and >90th, separately for male and female cohort members. These were available only for those with a gestational age of 30 through 43 weeks, numbers outside these ranges being too small for such categorization.

Occupational data were grouped into non-manual (social classes 1, 2 and 3 non-manual) and manual (social classes 3 manual, 4 and 5) groups using the appropriate Registrar General's Classification for the decennial census, 1961 for the parents of the cohort members and 1981 for the cohort members.

Cohort members were categorized as smokers or non-smokers at the beginning of pregnancy where the analysis was concerned with the effect of variables present before conception. Their mothers were similarly categorized by smoking habit at the beginning of pregnancy. Where the analysis was concerned with pregnancy effects smokers were only so categorized if they were still smoking by the fifth month or later since analyses of the original cohort have shown that only late smoking is related to birthweight (Butler *et al.* 1972).

Numbers in the analyses

The number of cohort members excluded because of missing data varied with different analyses and any stillborn or multiple births to them were excluded. In Table 1 an example is given of the exclusions which apply to the sample of the most recent births to the female cohort members, sequentially reducing the numbers to 880 used in Tables 2 and 3. The most recent birth to female cohort members (the only one for whom maternal smoking habit in pregnancy was known) was also the first born in 1165, the second born in 645, the third born in 127, the fourth born in 17, and the fifth in 3. There were 1366 corresponding births fathered by male cohort members, 1039 known to have been the first born. In their case it was not

Table 3. Multiple regression model prediction of F3 baby's birthweight (g) female cohort members—all most recent births

Sample size = 880
Final model

Significant predictor variable	Interval level	Regression coefficient	*t*-value
Constant	–	1563	–
F1 Grandmother's height	per 10 cm	53	2·03
F1 Grandfather's social class	manual *vs* non-manual	−93	−2·06
F2 Mother's birthweight	per 100 g	16	4·69
F2 Mother's non-pregnant weight	per 10 kg	92	4·86
F2 Mother's smoking at fifth month of pregnancy	yes *vs* no	−226	−6 68
F3 Baby's gender	female *vs* male	−143	−4·32
F3 Baby's birth order	second *vs* first	128	3·59
	third *vs* first	209	2·72
	fourth *vs* first	306	1·52

$R^2 = 0{\cdot}15$
$R = 0{\cdot}39$

Predictors dropped from 'Current' models, in descending order:	*t*-value
F2 Mother's weight *F2 Mother's smoking in pregnancy	0·48
F1 Grandfather's social class *F2 Father's social class	0·67
F1 Grandmother's non-pregnant weight per kg	0·18
F1 Grandmother: smoker *vs* non-smoker	−0·26
F2 Mother's adult height per cm	0·49
F2 Maternal age per months	−0·64
F2 Mother's gestation per days	−1·26
F2 Father's social class: manual *vs* non-manual	−1·80

Maximal model
$R^2 = 0{\cdot}16$
$R = 0{\cdot}40$

The regression coefficients of categorical variables give the mean difference in F3 birthweight relative to the lowest level of the variable. For example, the regression coefficients of F3 baby's birth order give the mean difference in F3 birthweight of 2nd, 3rd or 4th birth order babies relative to the 1st birth order.

* represents an interaction term.

necessary to limit analyses to the most recent births since no data had been collected on their partners' smoking habit.

For those analyses of the one baby only sample (used for Table 4), the number was reduced to 539 from a maximum of 1165; and for the analysis utilizing all first births (most recent and others) (used for Table 5) the number was reduced to 1027 from 1949 for babies of female cohort members, and 611 from 1366 for babies of male cohort members. The exclusions are of all generations of the case concerned so that whatever the biases introduced by such reductions they are unlikely to affect intergenerational relationships.

To simplify their description, parents of the cohort members are designated as the F1 generation, the cohort members as the F2, and their offspring as the F3 generation. The use of this genetic notation does not, however, imply that the relationships are necessarily, or actually genetic.

Table 2 gives an account of the predictor variables, their grouping and distribution, for the most important sample used: the most recent births to cohort members with full information.

Statistical methods

The effect of parental and grandparental characteristics on F3 birthweight was examined by multiple regression, using the statistical package GLIM. Model simplification was achieved by backward elimination from the maximal model. all models include a measure of 'goodness of fit', the squared multiple correlation coefficient R^2 representing the proportion of the variation in F3 birthweight explained by the predictor variables present in the model, and R which is the correlation between observed and fitted values of a model (Aitkin *et al.* 1989).

Interaction terms were added for variables commonly known to be strongly related with one another: mother's weight and her smoking habit; and social class of grandfather and father.

Results

Joint effects of grandparental and maternal characteristics

Table 3 shows the results of regressing the birthweight of the most recent babies of the cohort members (F3) on a number of grandparental and maternal characteristics. After adjustment for all variables present in the final model, statistically significant positive effects were the height of the grandmother (F1), each 10 cm adding 53 g to the weight of the grandchildren; the mother's (F2) non-pregnant weight, each 10 kg adding 92 g; the mother's own birthweight, each 100 g adding 16 g; and birth order, the mean increase of weight over the first born being 128 g for the second born, 209 g for the third, and 306 g for the fourth. Significant negative effects were having a grandfather (F1) in a manual occupation, which reduced birthweight of F3 by an average of 93 g; being of female sex, giving

Table 4. Multiple regression model prediction of F3 baby's birthweight (g) female cohort members—one baby only sample

Preconceptual model
Sample size = 539
Final model

Significant predictor variable	Interval/level	Regression coefficient	t-value
Constant	–	885	–
F1 Grandmother's height	per 10 cm	94	2·80
F2 Mother's birthweight	per 100 g	12	2·76
F2 Mother's non-pregnant weight	per 10 kg	108	4·35
F2 Mother's smoking at beginning of pregnancy	smoker *vs* non-smoker	−120	−2·70
F2 Father's social class	manual *vs* non-manual	−153	−3·02
R^2 = 0·12			
R = 0·35			

Predictors dropped from 'current' models, in descending order:	t-value
F1 Grandfather's social class *F2 Father's social class	0·43
F2 Mother's weight *F2 Mother's smoking in pregnancy	−0·49
F2 Mother's adult height per cm	0·33
F1 Grandmother: smoker *vs* non-smoker	−0·45
F2 Maternal age per months	−0·50
F1 Grandmother's non-pregnant weight per kg	0·79
F2 Mother's gestation per days	−1·46
F1 Grandfather's social class: manual *vs* non-manual	−1·61
Maximal model	
R^2 = 0·13	
R = 0·36	

* represents an interaction term.

a mean reduction of 143 g, and, most importantly, a mother (F2) who smoked after the fourth month of pregnancy, which on average reduced birthweight by 226 g. Gestational age of the mother (F2) did not have a significant effect, although it was negatively related, and mother's own height was not significant in this model which included grandmother's (F1) height and mother's (F2) birthweight. The final model 'explained' 15% of the variation of F3 birthweight.

Joint effects of grandparental and maternal preconceptional characteristics

Since the greatest challenge in predicting outcome relates to the first birth, models were then developed using only information available before the first pregnancy, and additionally including only those where the first had also been the most recent reported so that smoking history was available. In these analyses (Table 4) babies' sex is not used, and the categorization of maternal (F2) smoking was between smoking and not smoking at the beginning of pregnancy. In spite of these limitations 12% of the variation was 'explained'. Grandmother's height, mother's own birthweight, adult weight, and smoking habit, and father's social class remain significantly associated with an effect on in F3 birthweight.

Many mothers do not know their own birthweight or their gestational age exactly, but might know that they had been of low or normal birthweight. The effect of maternal birthweight on F3 birthweight remained statistically significant, and 11% of the variance remained 'explained' even after replacing birthweight as a continuous measure by a categorization of mothers as of birthweight <2500 g *vs* ≥2500 g. Again, grandmother's height was significantly associated with birthweight.

Joint effects of maternal, paternal and grandparental characteristics

Whatever comparable data were available for male cohort members were utilized to examine the joint effects of parental and grandparental effects in both maternal and paternal models. It must be remembered that only either the maternal or the paternal data were available, never that of both parents. Rather than using most recent births, these models used all first births since for these there were comparable data from both male and female cohort members.

A formal comparison of the effects of the paternal and maternal variables requires a joint model with tests for interaction that are inherently of low power. Such a model was constructed but these interactions were not significant so that the interpretation of maternal and paternal differential effects must be cautious. The findings in Table 5 are, however, consistent with the suggestion that the intergenerational influences through the maternal line are greater than through the paternal, since maternal grandparental factors were significant, but paternal grandparental factors were not. Nevertheless, paternal birthweight, and adult weight, but not social class, were significant influences on the birthweight of their babies.

Parental gestational age

In all maternal models there is a negative effect of F2 gestational age on F3 birthweight when examined jointly with the other variables, although this was statistically significant only in the model restricted to first births. This suggests that maternal birthweight for gestational age, a proxy for intrauterine growth rate, may be more important than birthweight *per se*. This suggestion was tested by replacing in the relevant

Table 5. Multiple regression models prediction of F3 baby's birthweight (g) female and male cohort members—all first births

Final model significant predictors	Interval/level	Regression coefficient		*t*-value	
		Female	Male	Female	Male
Sample size		1027	611	–	–
Constant		2244	2466	–	–
F2 Birthweight	per 100 g	19	14	5·23	3·15
F2 Adult weight	per 10 kg	86	50	4·57	2·43
F3 Baby's gender	female *vs* male	−109	−118	−3·30	−2·73
F2 Mother's gestation	per days	−4	–	−2·93	–
F1 Grandmother's height	per 10 cm	80	–	3·08	–
F1 Grandfather's social class	manual *vs* non-manual	−103	–	−2·33	–
F2 Father's social class	manual *vs* non-manual	−160	–	−4·07	–
R^2		0·11	0·05		
R		0·33	0·21		

Predictors dropped from 'current' models, in descending order:	
F2 female model	*t*-value
F1 Grandfather's social class *F2 Father's social class	0·75
F1 Grandmother's non-pregnant weight per kg	−0·04
F2 Adult height per cm	1·00
Maximal model	
$R^2 = 0{\cdot}11$	
$R = 0{\cdot}33$	
F2 Male model	
F1 Grandfather's social class *F2 Father's social class	0·37
F2 Father's social class: manual *vs* non-manual	0·01
F2 Grandfather's social class: manual *vs* non-manual	0·06
F2 Father's adult height per cm	0·63
F1 Grandmother's height per cm	−0·46
F2 Father's gestation per days	−0·83
F1 Grandmother's non-pregnant weight per kg	−1·45
Maximal model	
$R^2 = 0{\cdot}05$	
$R = 0{\cdot}23$	

*represents an interaction term.

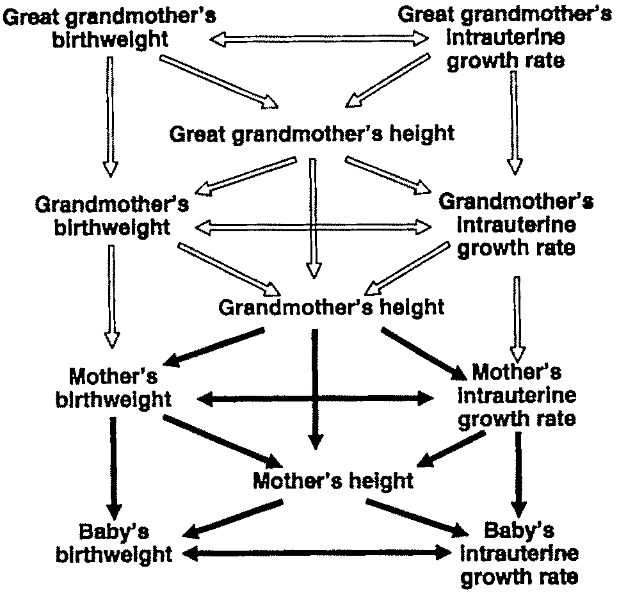

Great grandmother's birthweight
Great grandmother's intrauterine growth rate
Great grandmother's height
Grandmother's birthweight
Grandmother's intrauterine growth rate
Grandmother's height
Mother's birthweight
Mother's intrauterine growth rate
Mother's height
Baby's birthweight
Baby's intrauterine growth rate

Fig. 1. Patterns of relationships leading to the multigenerational influences on birthweight. (⇔) Hypothesized relationships; (⟷) relationships found in the British National Child Development Study.

models the continuous variables of birthweight and gestational age by the cruder, but still significant, categorization of birthweight centile for gestational age. The proportion of the variance in F3 birthweight 'explained' by these models was, if anything, slightly larger than when the two separate measures were used, and maternal grandmother's height was not then a significant factor.

Discussion

A substantial body of evidence has accumulated that indicates that how girls grow influences their reproductive outcomes when they are adults. The early evidence pertained to maternal stature, which, of course, is related both to genetic and non-genetic factors. Beginning with the Oxford studies (Ounsted & Ounsted 1968, 1973), the significant but complex relation between mother's and baby's intrauterine growth began to be recorded (Hackman *et al.* 1983; Toth *et al.* 1983; Klebanoff *et al.* 1984, 1989; Klebanoff & Yip 1987; Langhoff-Roos *et al* 1987). One study, based on small numbers of births in a tertiary centre, found an inverse relation between the mother's birthweight and her baby's need for neonatal intensive care and, specifically, for respiratory distress syndrome (Hackman *et al.* 1983).

In his last paper, Sir Dugald Baird concluded that ' . . . in the vulnerable social classes at least, three successive generations of mothers had high stillbirth rates from central nervous system malformations and in all probability from low birthweight,' and, further, that 'there is, of course a limit to what can be achieved in one generation in improving the level of health and physique . . .' (Baird 1985).

Intrauterine growth rate is also related to both genetic and non-genetic factors (Little & Sing 1987). Intrauterine growth, childhood growth adn adult stature are all strongly related to socioeconomic factors (Alberman *et al* 1991; Butler & Alberman, 1969; Wedge *et al.* 1970), and an intergenerational increase in adult stature is still seen in all social classes (Alberman *et al* 1991).

The present study offers more direct evidence for Baird's conclusions of at least a three generation influence on birth outcome, relating to both childhood social circumstances and childhood and ultimate adult growth.

However, it should be remembered that the current data are limited to births that had occurred to cohort members by the age of 23 years.

There were significant joint effects on the birthweight of the most recent births of mother's birthweight, and non-pregnant weight, grandmother's stature and grandfather's social class. Further, the model suggests that family circumstances under which the mother grew up are important in addition to the influence on the growth of the mother, grandfather's social class appearing to be if anything more important than father's social class, as also earlier reported by Drillien (1957). These intergenerational factors are significant in the presence of strong, long-established predictors of birthweight such as maternal smoking, baby's gender, and baby's birth order.

In practice it is perhaps most important to be able to predict birthweight and other outcomes of first pregnancies, where there is no previous reproductive history. The data (Table 4) show that in these also, grandmother's height and mother's birthweight are significant predictors, even without the additional information on the baby's sex and mother's smoking habit late in pregnancy.

While grandmother's height was usually significant in various models tested, and mother's non-pregnant weight was always significant, mother's stature and grandmother's weight were not. The heights of grandmothers and their daughters are reasonably strongly related so any model may be expected to include one or the other, but not both. The same may be true of non-pregnant weight of grandmothers and their daughters. It is of interest that the most significant relation is with grandmother's height. The measurement error introduced by crude categorization of her weight into stones (14 lbs) may also be a partial explanation of its exclusions from most of our models.

There is little information on the fathers of the babies of the female cohort members or on the mothers of the babies of the male cohort members, so that definitive comparisons of maternal and paternal effects are not possible. Nevertheless, the data in Table 5, where the same joint effects on baby's birthweight were examined in maternal and paternal models, are consistent with the previous work of Ounsted & Ounsted (1968, 1973), in which, with the exception of large for gestational age babies, the familial relation of birthweight and intrauterine growth rate were on the maternal side only. Johnstone & Inglis (1974) also found intrauterine growth trends related to the maternal line. Further, on a common sense basis, the mother provides both the genetic material and the intrauterine environment, while the father probably provides only nuclear genetic material.

Despite the extensive range of predictor variables that were fitted, the proportion of variation in F3 birthweight explained by any given model never exceeds 0·16. This is not surprising since the biological mechanisms determining birthweight are still far from understood. Although the statistical methods used are not comparable, this point is illustrated by the low correlation coefficient of 0·3 of even the well-recognized clinical association of pregnancy weight gain with birthweight (Hackman *et al.* 1983); of only 0·5 between birthweight and gestational duration in the perinatal phase of this 1958 cohort, and of 0·56 between the adult heights of the cohort members and their midparent height (Alberman *et al* 1991).

Our interpretation of the relationships leading to the intergenerational phenomenon is summarized in Fig. 1. We found that maternal grandmother's stature, itself likely to be influenced by her own intrauterine growth rate (Alberman *et al.* 1991), and by her environment in childhood (Wedge *et al* 1970), was consistently related to grandchild's birthweight. Thus there is evidence for at least a three generation and possibly longer influence on birthweight, and the data are consistent with the hypothesis that the most critical period of growth and development is the intrauterine period of the female embyro/fetus. A future communication derived from the present data will further address the importance of the mother's own intrauterine growth, and the current new follow-up of the cohort of the age of 32 will provide a larger set of data, which will include the gestational age of the babies of the cohort members as well as smoking habit in each pregnancy.

Because of the intergenerational phenomenon, it is clear that improvement in a population's reproductive outcomes will not be fully addressed simply by the provision of health services. Such improvement is probably partly dependent on the long term complex processes of improvement of fetal and child health, which accentuates the urgency to address these issues in a more comprehensive way. Short term goals are not enough.

Acknowledgments

This work was supported in part by: Grant No. 2800-5 from the Thrasher Research Fund, Grant No. HD23134 from the US National Institute of Child Health and Human Development, Grant No. MCJ-9043, from the Bureau of Maternal and Child Health and Resources Department, US Public Health Service. Dr Emanuel's sabbatical was supported by Senior International Fellowship No. F06 TWO 1274 from the Fogarty International Centre, National Institutes of Health. Appreciation is expressed to Professor John Fox and Mr Peter Shepherd of the Social Statistics Research Unit, City University, London.

References

Aitkin M., Anderson D , Francis B. & Hinde J. (1989) *Statistical Modeling in GLIM*, Clarendon Press, Oxford

Alberman E., Filakti H , Williams S., Evans S. J. W. & Emanuel I. (1991) Early influences on the secular change in adult height between the parent and children of the 1958 birth cohort. *Ann Hum Biol* **18**, 127-136.

Anderson W. J. R., Baird D. & Thomson A. M. (1958) Epidemiology of stillbirths and infant deaths due to congenital malformations. *Lancet* **i**, 1304-1306.

Baird D. (1947) Social class and foetal mortality *Lancet* **i**, 531-535.

Baird D. (1962) Environmental and obstetrical factors in prematurity, with special references to experience in Aberdeen. *Bull WHO* **26**, 291-295

Baird D. (1985) Changing problems and priorities in obstetrics. *Br J Obstet Gynaecol* **92**, 115-121.

Baird D. & Illsley R. (1952) Environment and childbearing. *Proc R Soc Med* **46**, 53-59.

Baird D. & Thomson A. (1969) The effects of obstetric and environmental factors on perinatal mortality by clinicopathological causes. In *Perinatal Problems The Second Report of the 1958 British Perinatal Mortality Survey* (Butler N. R. & Alberman E D., Eds), E & S Livingstone Ltd, Edinburgh, Scotland, pp 211-226

Barron S. L. (1974) Perinatal mortality and birthweight in Makassan, Indonesia *J Obstet Gynaecol Br Cmwlth* **81**, 187-195.

Butler N. R., Alberman E. D (eds) (1969) *Perinatal Problems· The Second Report of the 1958 British Perinatal Mortality Survey*. E & S Livingstone Ltd, Edinburgh, Scotland.

Butler N. R. & Bonham D. G. (1963) *Perinatal Mortality. The First Report of the 1958 British Perinatal Mortality Survey*, E & S Livingstone Ltd, Edinburgh, Scotland.

Butler N. R., Goldstein H. & Ross E. M. (1972) Cigarette smoking in pregnancy: Its influence on birth weight and perinatal mortality. *Br Med J* **2**, 127-130.

Chen Y. P., Chen H. Y. & Wei P. Y. (1963) Relationship between birthweight and height of mother *Assn Obstet Gynecol of the Republic of China* **2**, 1-8.

Drillien C. M. (1957) The social and economic factors affecting the incidence of premature birth. Part I—Premature births without complications of pregnancy. *J Obstet Gynaecol Br Emp* **64**, 161-184.

Emanuel I. (1986) Maternal health during childhood and later reproductive performance. *Ann NY Acad Sci* **447**, 27-38.

Emanuel I., Hale C. B., & Berg C. J. (1989) Poor birth outcomes of American black women: An alternative explanation. *J Public Health Policy* **10**, 299-308.

Hackman E., Emanuel I., van Belle G., Daling J. (1983) Maternal birthweight and subsequent pregnancy outcome. *JAMA* **250**, 2016-2019.

Hytten F. E. (1990) Long-term consequences of fetal deprivation. Commentary *Br J Obstet Gynaecol* **97**, 665-666.

Illsley R. (1955) Social class selection and class differences in relation to stillbirths and infant deaths. *Br Med J* **2**, 1523-1524.

Illsley R., Mitchell R. G. (eds). (1984) *Low Birthweight A Medical, Psychological and Social Study*. Wiley, New York.

Johnstone F. & Inglis L. (1974) Familial trends in low birth weight. *Br Med J* **3**, 659-661.

Kapur S., Kumar G., Mammen K. C. & Jesudian G (1971) Height and weight of South Indian women of childbearing age and their effect on birthweight and length of the baby. *Indian J Med Res* **59**, 1480-1488.

Kermack W D, McKendrick A. G. & McKinlay P. L. (1934) Death rates in Great Britain and Sweden. Some general regularities and their significance. *Lancet* **i**, 698-703.

Klebanoff M. A., Graubard B. I, Kessell S. S. & Berendes H. W. (1984) Low birthweight across generations. *JAMA* **252**, 2423-2427.

Klebanoff M. A. & Yip R. (1987) Influence of maternal birthweight on rate of fetal growth and duration of gestation *J Pediatr* **111**, 287-292.

Klenbanoff M. A., Mierik O & Berendes H. W. (1989) Second generation consequences of small-for-dates birth. *Pediatrics* **84**, 343-347.

Knight I. & Eldridge J (1984) *The Heights and Weights of Adults in Great Britain*. Office of Population Censuses and Surveys, Social Survey Division, Publication No. ISBN 0-11-691114X, Her Majesty's Stationery Office, London.

Langhoff-Roos J., Lindmark G., Gustavson K.-H., Gebre-Medhin M. & Mierik O. (1987) Relative effect of parental birthweight on infant birthweight at term. *Clin Genet* **32**, 240-248.

Lechtig A., Delgado H., Lasky R., Yarborough C., Klein R. E., Habicht J.-P. & Behar M. (1975) Maternal nutrition and fetal growth in developing countries. *Am J Dis Child* **129**, 553-556.

Little R. E. & Sing C. F. (1987) Genetic and environmental influences on human birthweight. *Am J Hum Genet* **40**, 512-526.

Martorell R., Delgado H. L, Valverde V. & Klein R. E. (1981) Maternal stature, fertility, and infant mortality. *Hum Biol* **53**, 303-312.

Ounsted M. & Ounsted C. (1968) Rate of intrauterine growth. *Nature* **220**, 599-600.

Ounsted M. & Ounsted C. (1973) On fetal growth rate. *Clin Dev Med* **46**, 65-68

Shepherd P. M. (1985) *The National Child Development Study An Introduction to the Background to the Study and the Methods of Data Collection* National Child Development Study User Support Group, Working Paper No. 1, Social Statistics Research Unit, City University, London.

Singer B., Blake L. & Wolfsdorf J. (1973) Comparative study of African and white liveborn infants. *S Afr Med J* **47**, 2399-2402

Thomson A. M. (1959) Maternal stature and reproductive efficiency. *Eugen Rev* **51**, 157-162.

Toth P., Keszen K. & Mehes K. (1983) Maternal regulation of fetal growth. *Acta Paediatr Hung* **24**, 37-48.

Wedge P., Alberman E. & Goldstein H (1970) Health and height in children. *New Society* **16**, 1044-1045.

Received 18 March 1991
Accepted 7 August 1991

British Journal of Obstetrics and Gynaecology
January 1992, Vol. 99, pp. 75–80

CASE REPORTS

Prospective modulation of platelet function and volumes by aspirin and dipyridamole in an at-risk pregnancy

M. H. F. SULLIVAN
L. FUSI
J. BROSENS
M. G. ELDER

Institute of Obstetrics and Gynaecology, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0HS, UK

Case report

A 42-year-old woman was referred in March 1990 to the gynaecology clinic for investigation of recurrent miscarriages. She had had a deep vein thrombosis and there was a strong family history of cardiovascular disease. She had a first miscarriage in 1987 at 6 weeks and a missed miscarriage in 1988 at 20 weeks gestation. In November 1989 she had another second trimester miscarriage at 20 weeks. The fetuses were small for gestational age but were otherwise normal. All pregnancies were with the same partner. The placental histology on the most recent pregnancy loss was reported as showing a remarkable similarity to that seen in patients with lupus or anticardiolipid syndrome, but a lupus anticoagulant screen was negative and cardiolipin antibodies were within the normal range. An extensive clotting screen was normal but it was noted that during her pregnancies she had consistently low platelet levels (150–170 × 10^9/l) declining to 90 × 10^9/l at the time of her second miscarriage in 1988. Pre-conception investigations revealed that she had a high haematocrit (0·459) and haemoglobin levels (15·1 g/dl), together with a high mean platelet volume (assessed using Sysmex 2000 monitor, Toa Medical Electronics). In vitro platelet aggregation in response to platelet-activating factor (Ahmed *et al.* 1991a) was normal. Full platelet resynthesis (determined as described by Patrignani *et al.* 1982) required about 4 days, compared with the normal 8–10 days (Rakoczi *et al.* 1979). In view of these results showing increased platelet turnover, she was treated with low-dose aspirin (75 mg daily).

In September 1990 she became pregnant for the fourth time and the platelet numbers, volume indices and aggregation response *in vitro* were monitored every 2 weeks during pregnancy. The haematocrit and platelet volumes remained constant during early pregnancy, but in vitro platelet responses to platelet-activating factor and ADP suggested increased activation so, at 8 weeks gestation, the phosphodiesterase inhibitor dipyridamole (200 mg, thrice daily) was added to the low dose aspirin. Haemoglobin levels and the haematocrit declined with the addition of dipyridamole and remained within the normal range until delivery. Platelet reactivity to ADP and platelet activating factor decreased subsequently, and remained relatively constant for the next 22 weeks. Platelet numbers remained at the lower end of the normal range, and platelet volumes fell and then remained almost unchanged until 29 weeks gestation. At this time platelet volumes increased markedly, and platelet numbers decreased to 150 × 10^9/l (Fig. 1). This increase in volume was sustained for 1 week, after which dipyridamole was increased to 200 mg four times daily and platelet volumes decreased in response to the change in medication. One week later (32·4 weeks gestation), platelet volumes reached their highest levels recorded up to this point, so the aspirin treatment was changed from 75 mg daily to 50 mg twice daily. Platelet volumes decreased and platelet numbers increased immediately and only changed gradually over the next 3 weeks. A further increase in platelet volumes (to 13·1 fl) and a decline in platelet numbers to 120 × 10^9/l at 36 weeks gestation, together with increasing *in vitro* responses to ADP suggested an increase in platelet activation and led to the decision to deliver her by elective caesarean section. Dipyridamole and aspirin were stopped pre-operatively and a healthy male infant weighing 2500 g was born. Post-operatively, subcutaneous heparin (7500 IU twice daily) was given for 6 weeks. The puerperium was uneventful, with platelet indices returning to pre-pregnancy values (Fig. 1).

Throughout this pregnancy the patient remained normotensive (blood pressure <140/90 mmHg) without proteinuria. Serial ultrasound scans showed adequate fetal growth and regular Doppler flow studies remained normal. The placenta was of a normal size (16 cm × 17 cm) and weight (440 g), but one small haemorrhage was visible. Detailed investigation was consistent with placental ischaemia, and also showed a thrombus and fibrin deposition within a fetal vessel.

Discussion

This patient's platelets showed increased platelet aggregation *in vivo*, although the extent to which this had contributed to the three consecutive early pregnancy losses cannot be assessed accurately. It has been shown that many early miscarriages are associated with deficient trophoblastic growth (Hustin *et al.* 1990), and similar pathology has been described for gestational hypertension, pre-eclampsia and fetal growth retardation (Robertson *et al.* 1975). On the basis that low-dose aspirin and dipyridamole may be of benefit in these disorders (Beaufils *et al.* 1985; Wallenburg *et al.* 1986; Trudinger *et al.* 1988), the same therapy was used in our patient. Clinically, the pregnancy progressed satisfactorily, in that fetal growth, ultrasound measurements and maternal health remained normal. Previous studies in general populations have not shown any obvious benefit of dipyridamole and aspirin over aspirin alone (Beaufils *et al.* 1985; Wallenburg *et al.* 1986; Uzan *et al.* 1991), but our findings suggest that dipyridamole may be a useful

Correspondence: M. H. F. Sullivan.

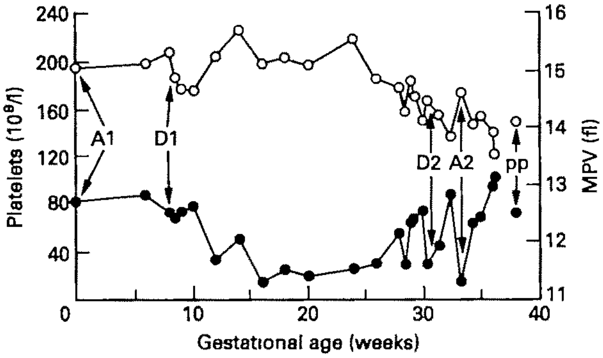


Fig. 1. Changes in platelet numbers (○) and mean platelet volume (MPV) (●) with gestational age and different drug therapy. A1: aspirin (75 mg/day); A2: aspirin (50 mg twice daily); D1: dipyridamole (200 mg thrice daily); D2· dipyridamole (200 mg four times daily). pp: post-partum. 0: not pregnant.

adjunct to aspirin in some patients in whom aspirin alone is not sufficient to suppress platelet aggregation adequately.

Platelet aggregation *in vitro* changed during pregnancy, showing a trend towards increased responsiveness during the last trimester, and this was accompanied by marked changes in platelet volumes during the same period. Changes in medication (increased aspirin and dipyridamole) were accompanied by decreases in platelet volumes and in platelet responses, suggesting that the increasing reactivity of the platelets later in this pregnancy could to some extent be counteracted by increasing the anti-platelet therapy. The twice-daily aspirin treatment was used on the following assumptions. Under normal circumstances, a single low-dose aspirin decreased serum thromboxane B2 by 50% (Sullivan *et al.* 1990), after which 10% recovery would occur in the subsequent 24 h (Rakoczi *et al.* 1979); repeated aspirin treatment therefore decreases platelet thromboxane synthesis by 90%. In our patient, about 25% of the total platelets would be resynthesized within 24 h (platelet recovery within 4 days), so the maximum inhibition of thromboxane production on daily aspirin would be between 50% and 75%, compared with 75–87·5% on a twice daily dose. It is difficult to determine the extent to which the success of this pregnancy depended on the anti-platelet therapy, but, given her previous obstetric experience, the evidence of platelet abnormalities before pregnancy, and the major changes in platelet function, numbers and volume in later pregnancy, it seems likely that the therapy used was appropriate. The evidence of placental thrombus formation was consistent with the increasing platelet turnover during the third trimester.

In conclusion, we have found that aspirin plus dipyridamole may be a useful combination of anti-platelet drugs in some women with high platelet turnover in whom aspirin alone (Ahmed *et al.* 1991b) is insufficient to allow normal pregnancy. In addition, changes in platelet volume give additional information on in vivo platelet function, and may be of use in the monitoring of at-risk pregnancies. It may be that changes in platelet volumes rather than absolute volumes are the best indicator of altered platelet behaviour in vivo, since there was no obvious correlation between the in vitro responses (to platelet activating factor and ADP) and measured platelet volumes, but further studies are required.

References

Ahmed Y., Sullivan M. H. F. & Elder M. G. (1991a) Detection of platelet desensitization in pre-eclampsia is dependent on the agonist used. *Thromb Haemost* **65,** 474–477.

Ahmed Y., Sullivan M. H F. & Elder M. G. (1991b) Increased platelet turnover in a patient with previous recurrent pre-eclampsia and failure of aspirin therapy. *Br J Obstet Gynaecol* **98,** 218-220.

Beaufils M., Uzan S., Donsimoni R. & Colau J. C. (1985) Prevention of pre-eclampsia by early antiplatelet therapy. *Lancet* **i,** 840-842.

Hustin J., Jauniaux E. & Schaaps J. P. (1990) Histological study of the materno-embryonic interface in spontaneous abortion. *Placenta* **11,** 477-486.

Patrignani P., Filabozzi P. & Patrono C. (1982) Selective cumulative inhibition of platelet thromboxane production by low dose aspirin in healthy subjects. *J Clin Invest* **65,** 1366-1372.

Rakoczi I., Tallian F., Bagdany S & Goti I. (1979) The platelet lifespan in normal pregnancy and pre-eclampsia. *Thromb Res* **15,** 553-556.

Robertson W. B., Brosens I. & Dixon G. (1975) Uteroplacental vascular pathology. *Europ J Obstet Gynaecol Reprod Biol* **5,** 47-65.

Sullivan M. H. F., Zosmer A., Gleeson R. P & Elder M. G. (1990) Equivalent inhibition of *in vivo* platelet function by low dose and high dose aspirin treatment. *Prostaglandins Leukot Essent Fatty Acids* **39,** 319-321.

Trudinger B. J., Cook C. M., Thompson R. S., Giles W. B & Connelly A. (1988) Low-dose aspirin therapy improves fetal weight in umbilical placental insufficiency. *Am J Obstet Gynecol* **159,** 681-685.

Uzan S., Beaufils M., Breart G , Bazin B., Capitant C. & Paris J. (1991) Prevention of fetal growth retardation with low-dose aspirin. *Lancet* **337,** 1427-1431.

Wallenburg H. C. S., Dekker G. A , Makovitz J. W. & Rotmans N. (1986) Low-dose aspirin prevents pregnancy-induced hypertension and pre-eclampsia in angiotensin-sensitive primigravidae. *Lancet* **i,** 1-3.

Received 19 July 1991
Accepted 25 September 1991

British Journal of Obstetrics and Gynaecology
January 1992, Vol. 99, pp. 77–79

Severe non-diabetic keto-acidosis causing intrauterine death

J. M. LAND
Nuffield Department of Clinical Biochemistry
C. H. D. A'COURT
M. D. G. GILLMER
Nuffield Department of Obstetrics and Gynaecology
J. G. G. LEDINGHAM
Nuffield Department of Medicine
University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU

Case report

A 22-year-old woman (pre-pregnancy weight 52 kg and body mass index 19·1) with a twin pregnancy at 32 weeks gestation (pregnancy weight gain 14·1 kg) was referred in preterm labour from a peripheral hospital where she had been given a single subcutaneous dose of terbutaline 250 μg, a beta-adrenoceptor stimulant (β-agonist). Painful uterine contractions were continuing when she arrived in Oxford. Intravenous ritodrine, another β-agonist, was therefore begun at 50 μg/min, increasing over 1 h to 150 μg/min until the contractions stopped. Over the next 2 h the infusion rate was reduced to 50 μg/min and was continued at this dose for a further 10 h. Subsequently, to reduce the likelihood of further contractions, oral salbutamol 8 mg 8-hourly was prescribed.

Apart from a transient tachycardia in Twin II at the higher ritodrine infusion rate, there was no cardiotocographic evidence of fetal distress. However, while on oral salbutamol the woman developed nausea and vomiting and intermittent tachypnoea. The salbutamol was therefore stopped after four doses. Over the following 12 h severe maternal distress, hyperventilation and confusion developed. Blood gas analysis showed a profound acidaemia due to a metabolic acidosis with incomplete respiratory compensation. Arterial blood gas values were pH 7·02, $P\text{CO}_2$ 0·9 kPa, $P\text{O}_2$ 19 kPa and base excess −28·8 mEq/l while the patient breathed air. Her blood glucose was 3·7 mmol/l. A screening blood glucose earlier in the pregnancy had been normal and glycated haemoglobin (5·9%) was not raised. There was no clinical or biochemical evidence of renal or liver failure. She denied ingestion of drugs or toxins and salicylate was not detected in the plasma. When the acidosis was noted neither of the fetal heart beats could be detected with a fetal heart monitor and intrauterine death of both twins was confirmed by ultrasound scanning. Although the woman was apyrexial and she had a normal blood pressure and normal urine output, the possibility of septicaemia causing lactic acidosis and intrauterine death was considered. An elevated white cell count of 23 × 10^9/l with a neutrophil leucocytosis appeared to support this diagnosis.

She was transferred to the intensive care unit where she received intravenous infusions of 4·2% sodium bicarbonate, 400 ml and 5% dextrose 100 ml/h, together with intravenous ampicillin, gentamicin and metronidazole. When her condition had stabilized, labour was induced by artificial rupture of membranes and an intravenous oxytocin infusion. Two fresh stillborn fetuses were born and on postmortem examination they were found to be normal except for scattered petechial haemorrhages. The woman's condition rapidly improved and her arterial blood pH returned to normal within 24 h without further intervention.

Subsequent investigations did not provide any evidence of septicaemia but they did suggest a possible metabolic aetiology. Cultures of maternal blood, urine and amniotic fluid and of fetal material were all negative, as was serology for hepatitis A and B, cytomegalovirus, toxoplasma, rubella and listeria. Blood lactate was only marginally raised at 2·9 mmol/l. Ward urinalysis had shown marked ketonuria. Subsequent organic acid analysis (high performance liquid chromatography and gas chromatography/mass spectrometry) showed only aceto-acetate and 3-hydroxybutyrate and no other abnormal organic aciduria. Plasma 3-hydroxybutyrate was markedly raised at 9·7 mmol/l with a 3-hydroxybutyrate/aceto-acetate ratio of 1, giving a total ketone body concentration of 19·4 mmol/l. These values are markedly raised. Typical total ketone body concentrations in normal non-pregnant subjects are 0·1 mmol/l after an overnight fast, 3 mmol/l after 3 days fasting, and 9 mmol/l after 25 days fasting. In diabetic keto-acidosis total ketone body concentrations of 7–8 mmol/l are often found; only very rarely have levels up to 20 mmol/l been recorded (Newsholme & Leach 1983).

In addition, it was noted that the plasma amino acid profile at the height of the metabolic disturbance showed no evidence of hypo-aminoacidaemia. In particular, gluconeogenic precursors (alanine 393 μmol/l, valine 339 μmol/l, leucine 273 μmol/l and isoleucine 82 μmol/l), were not decreased. The limited supply of substrates for gluconeogenesis normally observed during starvation in early (Tyson *et al* 1976) and late pregnancy (Metzger *et al.* 1982) was therefore not responsible for the profound ketogenesis observed. It was concluded that the severe keto-acidosis was due to inadequate dietary intake and β-agonist therapy in the presence of a twin pregnancy. However, we could not exclude the possibilities that the woman was either extraordinarily sensitive to β-agonists, or suffering from an inherited defect of ketolysis. Accordingly, she was re-admitted to hospital about 6 months later and her responses to an oral glucose tolerance test, administration of a β-agonist (salbutamol) and starvation were studied. Her blood glucose and insulin responses to an oral glucose tolerance test were entirely normal. Her blood growth hormone, insulin, glucose, free fatty acid and lactate levels in response to the intra-

Correspondence: J. M. Land.

venous administration of 100 μg salbutamol were also normal (Goldberg *et al* 1975). Similarly, starvation produced an appropriate ketonaemic response, mobilization of free fatty acids, suppression of insulin release and normal urinary organic acid and plasma amino acid profiles.

Comment

Keto-acidosis in pregnancy is usually a manifestation of uncontrolled diabetes mellitus and has a well-recognized association with intrauterine deaths (Hall & Tilmon 1951). β-Agonists, used in the management of preterm labour, are known to cause keto-acidosis in diabetics (Leslie & Coates 1977; Tibaldi *et al.* 1990).

The marked ketonaemia observed in our patient is worthy of comment and explanation.

In pregnancy, rapid mobilization of maternal fat stores and the generation of hyperketonaemia in response even to short periods of fasting is seen. This phenomenon, termed accelerated starvation, appears to provide ketones as substrate for the pregnant woman while sparing glucose and amino acids for fetal utilization (Metzger *et al.* 1982). At the same time, the ketonaemia may play a role in preservation of maternal muscle mass since ketone bodies appear to lower the rate of muscle protein degradation (Owen *et al.* 1990). This process is characterized by raised plasma free fatty acid levels, increased plasma and urinary ketones, hypo-insulinaemia and hypo-aminoacidaemia. In part, the process is self-sustaining since the changes in the plasma amino acids, particularly alanine and the branch chain amino acids, inhibit hepatic gluconeogenesis by limiting substrate availability. In contrast to the non-pregnant state, marked metabolic adaptation may be seen after as little as 18 h fasting in late pregnancy with β-hydroxybutyrate levels rising to 0·5 mmol/l or more, three times the baseline concentrations (Metzger *et al.* 1982). After fasting for longer periods the differences in ketonaemia between the pregnant and non-pregnant state appear to be less pronounced. In one study differences between pregnant and non-pregnant women were no longer discernible after 84 h of fasting (Felig & Lynch 1970). However, although absolute ketone body concentrations were raised at about 5 mmol/l, the concentrations observed in that study were considerably less than we observed in our patient.

The balance between the fetal and maternal benefits of accelerated starvation and the detrimental effects to the fetus of enhanced ketonaemia may be a fine one. It has been suggested that chronic ketonuria during pregnancy may be associated with impaired intellectual development in the offspring (Stehbens *et al.* 1977). In addition fetal death due to keto-acidosis has been reported (Schilthuis & Aarnoudse 1980). The absolute levels of ketone bodies in these and other cases described were markedly less than the values we observed. We believe that the maternal metabolic demands made by the twin pregnancy during the period of 'fasting' were substantial. However, the metabolic response was not typical of simple starvation since she did not show a deficiency of amino acid gluconeogenic precursors and her hypoglycaemia was mild, yet her hyperketonaemia was massive. We suggest, therefore, that a second factor, the metabolic effect of the β-agonist, may have contributed to our patient's profound ketoacidaemia.

β-Agonists are widely used in the management of preterm labour. They relax uterine smooth muscle and may also cause concomitant metabolic effects, depending upon the dose and duration of usage. The effects of β-agonists have been studied in non-pregnant and pregnant diabetic and non-diabetic subjects. In non-diabetics, salbutamol, a selective β_2-agonist, stimulates lipolysis producing marked, rapid rises in plasma free fatty acids, ketones and insulin and smaller but discernible increases in glucose and lactate (Goldberg *et al.* 1975). In diabetics the insulin response is minimal and accordingly the glycaemic and ketonaemic responses are greater. In diabetic pregnancies β-agonists have been noted to cause ketonuria and metabolic acidosis when used to control preterm labour (Van Lierde *et al.* 1982) and in at least one case intrauterine death has occurred (Schilthuis & Aarnoudse 1980). Severe keto-acidosis complicating β-agonist therapy in a non-diabetic patient does not appear to have been described previously.

Conclusion

Keto-acidosis of the degree seen in our patient has not previously been reported in a non-diabetic pregnant woman. We believe that in this case the normal counter-regulatory responses to starvation which in pregnancy are already accelerated were further accentuated by the patient's small body mass, inadequate dietary intake for the metabolic demands of a twin pregnancy and the metabolic consequences of prolonged β-agonist therapy. Additionally, we could find no evidence of either undue sensitivity to the β-agonist salbutamol nor any evidence of an inborn error of metabolism affecting ketolysis. The vigorous ketogenesis provoked by starvation and β-agonist administration in pregnancy needs to be recognized in the management of preterm labour.

References

Felig P & Lynch V. (1970) Starvation in human pregnancy: hypoglycaemia, hypoinsulinaemia, and hyperketonemia. *Science* **170,** 990-992.

Goldberg R., van As M., Joffe B. I., Krut L., Bersohn I. & Seftel H. C. (1975) Metabolic responses to selective β-adrenergic stimulation in man. *Postgrad Med J* **51,** 53-58.

Hall R. E. & Tilmon A J. B. (1951) Diabetes in pregnancy. *Am J Obstet Gynecol* **61,** 110-115.

Leslie D. & Coates P. M. (1977) Salbutamol induced diabetic ketoacidosis. *Br Med J* **ii,** 768.

Metzger B. E., Ravnikar V., Vileisis R. & Freinkel N. (1982) 'Accelerated starvation' and the skipped breakfast in late normal pregnancy. *Lancet* **i,** 588-592

Newsholme E. A. & Leach A. R. (1983) *Biochemistry for the Medical Sciences* John Wiley and Sons, pp. 284-285.

Owen D. E., Tappy L., Mozzoli M A. & Smalley K. J. (1990) In *The Metabolic and Molecular Basis of Acquired Disease* (Cohen R. D., Lewis B., Alberti K. G. M. M. & Denman A. M., eds), Baillière Tindall, pp. 550-570.

Schilthuis M. S. & Aarnoudse J. G. (1980) Fetal death associated with severe ritodrine induced ketoacidosis. *Lancet* **i,** 1145.

Stehbens J. A., Baker G. L. & Kitchell M. (1977) Outcome at ages 1, 3 and 5 years of children born to diabetic women. *Am J Obstet Gynecol* **127,** 408-413.

Tibaldi J. M., Lorder D. L. & Nerenberg A. (1990) Diabetic ketoacidosis and insulin resistance with subcutaneous terbutaline infusion: A case report. *Am J Obstet Gynecol* **163**, 509-510.
Tyson J. E., Austin K., Farinholt J. & Fielder J. (1976) Endocrine-metabolic response to acute starvation in human gestation. *Am J Obstet Gynecol* **125**, 1073-1084.
Van Lierde M., Buysschaert M., de Hertogh R., Loumaye R. & Thomas K. (1982) Intravenous administration of ritodrine to pregnant insulin-dependent diabetics. Metabolic impact. *J Gynecol Obstet Biol Reprod* **11**, 869-875.

Received 15 April 1991
Accepted 8 August 1991

British Journal of Obstetrics and Gynaecology
January 1992, Vol. 99, pp. 79–80

Pregnancy complicated by Charcot-Marie-Tooth disease, requiring intermittent ventilation

D. L. BYRNE
Research Fellow

O. A. CHAPPATTE
Senior Registrar

G. T. SPENCER
Consultant in Respiratory Medicine

K. S. RAJU
Consultant Obstetrician

Departments of Obstetrics and Lane Fox Respiratory Unit, St Thomas' Hospital, London SE1 7EH

Case report

A 26-year-old married women, who from the age of five years had suffered from Charcot-Marie-Tooth disease (hereditary motor and sensory neuropathy type 1), was referred for an obstetric opinion in her first pregnancy at 13 weeks gestation. The neuropathy had caused wasting of her limbs and trunk and a 30° lumbar scoliosis. At 24 years of age she had developed respiratory insufficiency with severe nocturnal hypoventilation (nocturnal $Pa\mathrm{CO}_2 = 80$ mmHg; forced vital capacity = 500 ml). Her small size and limb weakness made non-invasive respiratory aid impractical and a tracheostomy was performed. For 2 years thereafter she maintained normal blood gas tensions, breathing spontaneously by day and receiving artificial respiration from an East Radcliffe respirator via a non-cuffed silver tracheostomy tube (Gilston 1967) by night.

At the time of referral she weighed 24·2 kg and had been wheelchair bound for 4 years. Although the pregnancy was unplanned she would not consider termination unless the pregnancy was expected to 'kill her'. Both she and her husband had received genetic counselling and understood there was a 50% chance of the fetus being affected.

She was electively admitted to the respiratory unit at 22 weeks gestation to manage the increasing respiratory dependence (Fig. 1). As pregnancy progressed air leakage around the tracheostomy tube increased due to rising inflation pressures. This eventually necessitated a cuffed tracheostomy tube at 29 weeks and as pregnancy progressed the proportion of time on

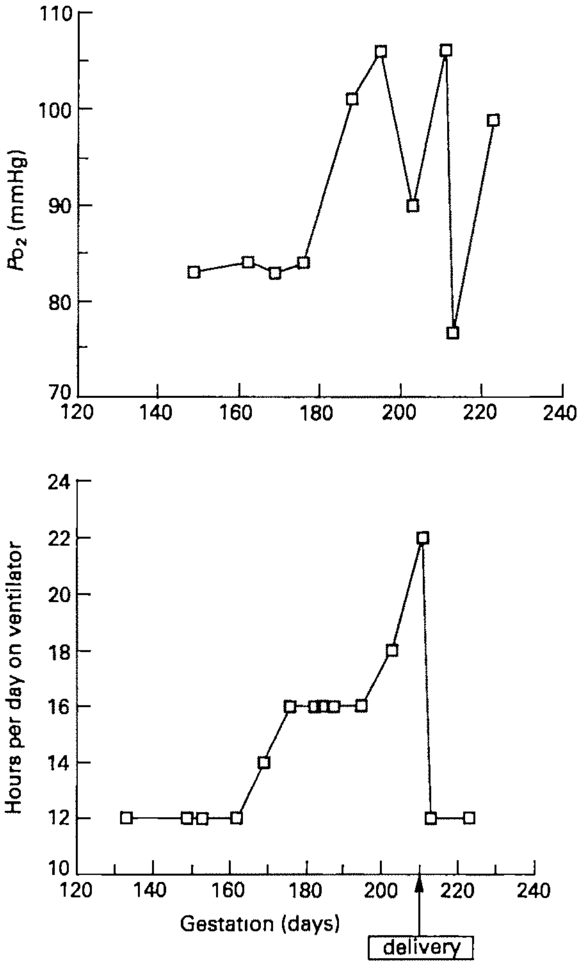


Fig. 1. Changes in maternal arterial $P\mathrm{O}_2$ and hours per day on artificial ventilation with advancing pregnancy.

Correspondence: Mr D. L. Byrne, Department of Obstetrics.

artificial ventilation was increased, to maintain normal arterial blood gas tensions.

Ultrasound scans demonstrated normal fetal anatomy and growth along the 40th centile for fetal abdominal and head circumference. Serial Doppler flow velocity waveforms were normal throughout pregnancy. At 30 weeks gestation spontaneous labour began and she was delivered by lower segment caesarean section under general anaesthesia. A liveborn female infant, weighing 1410 g (50th centile for birthweight) was born by the breech and transferred to the special care nursery.

Postoperative recovery was uneventful and maternal artificial respiratory requirements rapidly decreased to her normal needs by the time she was discharged at 12 days postpartum. The neonatal course was complicated by necrotizing enterocolitis which, although responding to conservative treatment, resulted in a colonic stricture requiring laparotomy and resection. The baby was discharged at 3 months of age, doing well.

Discussion

Hereditary motor and sensory neuropathy type 1 or Charcot-Marie-Tooth disease is a slowly progressive peripheral neuropathy which usually presents in the first decade of life with weakness of the lower limbs and difficulty walking. Muscle wasting and early loss of tendon reflexes are characteristic and the condition progresses to the hands and trunk. The disease is inherited as an autosomal dominant and does not deteriorate in pregnancy (Harding & Thomas 1980; Massey & Cefalo 1977), although respiratory difficulties may be worsened due to the increased respiratory demands of pregnancy.

There is no direct effect on the fetus (excepting inheritance of the disease), but there may be secondary effects from maternal respiratory compromise. In our patient neuropathy and muscle wasting prevented adequate maternal respiration and increasing periods of artificial ventilation were required to maintain normal ventilation.

Kopenhager (1977) noted an association between scoliosis in pregnancy and intrauterine growth retardation and suggested it was due to poor maternal oxygenation. In our patient ventilation was strictly monitored by maternal blood gas tension measurements and fetal growth was normal.

Distortion of the maternal chest and lumbar spine increases the risk of malpresentation and makes epidural anaesthesia more difficult. The breech presentation in conjunction with maternal weakness and pelvic deformity were the indications for caesarean section, although vaginal delivery has been described (Bellina & Deming 1973) and is suitable in less severely affected women.

This is the first report of artificial ventilation in a pregnancy complicated by Charcot-Marie-Tooth disease and illustrates that with careful maintenance of normal ventilation by mechanical assistance as necessary, a successful outcome may be expected.

Investigation of the baby to establish if she is affected will be carried out by nerve conduction studies at 6 months of age.

Acknowledgment

Dominic Byrne is supported by a grant from The St Thomas' Baby Fund.

References

Bellina J & Deming B (1973) Charcot-Marie-Tooth disease and pregnancy. Report of a case. *J La State Med Soc* **125**, 393-395.

Gilston A. (1967) Modifications of the Negus tracheostomy tube. *Lancet* **i**: 1326.

Harding A E. & Thomas P. K. (1980) The clinical features of hereditary motor and sensory neuropathy types 1 and 2. *Brain* **103**, 259-280.

Kopenhager T (1977) A review of 50 pregnant patients with kyphoscoliosis. *Br J Obstet Gynaecol* **84**, 585-587.

Massey E. W. & Cefalo R. C. (1977) Neuropathies of pregnancy *Obstet Gynaecol Surv* **34**, 489-492

Received 23 November 1990
Resubmitted 20 May 1991
Accepted 18 June 1991

British Journal of Obstetrics and Gynaecology
January 1992, Vol. 99, pp. 81–84

SHORT COMMUNICATIONS

Transilluminating ureteric stents for preventing operative ureteric damage

J. H. PHIPPS
Consultant Obstetrician & Gynaecologist

George Eliot Hospital, College Street, Nuneaton, Warwickshire CV10 7BL

N. J. TYRRELL
Technical Officer

Rocket of London Limited, Watford, Herts WD2 4XX

The frequency of damage to the ureter as a complication of abdominal hysterectomy is reported to be as high as 1·5% (Daly & Higgins 1988). Complications are more likely if the patient has undergone previous surgery, if the anatomy is distorted, or in the presence of gross pelvic adhesions. Oophorectomy after previous hysterectomy is especially hazardous, since any cyst in the ovary may have grown retroperitoneally, so that the ureter may overlie the cyst and be vulnerable to surgical damage.

With the increasing popularity of laparoscopic surgery, particularly in conjunction with the neodymium-yttrium-aluminium-garnet (Nd–YAG) laser, ureteric damage due to inadvertent heating where it lies close to the peritoneal surface is likely to become more common. Ureteric injury complicating laparoscopic surgery has been reported after both diathermy and laser surgery for endometriosis (Cheng 1976; Gomel & James 1991), tubal sterilization (Dowling *et al.* 1986) and electrocoagulation of the uterosacral ligaments (Irvin *et al.* 1975).

There is a zone of tissue necrosis several millimetres beyond that which is immediately apparent after exposure to either diathermy (Indman & Soderstrom 1990) or YAG laser (Goldrath 1987; Rosenberg *et al.* 1990) and the surgeon may overestimate the safety margin when ablating tissue near the site of the ureters. Although the ureters may be identified manually in open surgery (sometimes with great difficulty), this is impossible during laparoscopic surgery.

The device described here was designed to reduce the likelihood of ureteric damage during complex open surgery or ablative laparoscopic surgery.

Device and method

The luminescent ureteric stent is a 2 mm diameter flexible, multistrand fibre optic rod, which can be connected to a standard high-intensity cold light source via a standard light-cable used for endoscopy. The catheter is passed down the operating channel of a cystoscope and inserted under direct vision into the ureteric orifice. The distal 200 mm of the catheter illuminates at 10 mm intervals but the remainder of the fibre optic rod does not, acting as a light transmitter to the 'active' tip. The proximal end is connected to the cold light source and the stent is illuminated just before surgery. No serious heating of the stent occurs (tested up to 1 h continuous use).

Laparoscopically, the ureters are visible as glowing lines either side of the uterosacral ligaments and along the pelvic side-wall. During open surgery, in the presence of anatomical distortion and dense adhesions, the ureters may not be detected immediately. However, as dissection proceeds, close proximity to them is signified by the appearance of the glow, warning the surgeon before any damage occurs.

Correspondence: J. H. Phipps

Comment

Luminescent ureteric stents may reduce the risk of ureteric injury during complicated open or laparoscopic surgery. The disadvantages are that the gynaecologist must learn the skills necessary for cystoscopic placement of the stents, the time added to the duration of the operation, and the cost of the stents. However, the morbidity and financial cost of ureteric injury are such that any reduction in the occurrence of this complication must be welcome.

References

Cheng Y S. (1976) Ureteral injury resulting from laparoscopic fulguration of endometriotic implant, *Am J Obstet Gynecol* **126** (8) 1045-1046.

Daly J. W. & Higgins K. A. (1988) Injury to the ureter during gynaecologic surgical procedures, *Surg Gynaecol Obstet* **167**, 19-22.

Dowling R. A., Corriere J. N., Jr & Sandler C. M. (1986) Iatrogenic ureteral injury, *J Urol* **135**, 912.

Goldrath M. H. (1987) Nd–YAG laser/tissue interactions In *Gynaecological Laser Surgery*, (Sharp F. & Jordan J. A , eds), Perinatology Press, New York, pp. 59–63.

Gomel V & James C. (1991) Intraoperative management of ureteral injury during laparoscopic surgery, *Fertil Steril* **55** (2), 416–419

Indman P. D & Soderstrom R. M (1990) Depth of endometrial coagulation with the urologic resectoscope, *J Reprod Med* **35** (6), 633–635.

Irvin T. T, Goligher J. C. & Scott J. S. (1975) Injury to the ureter during laparoscopic tubal sterilisation, *Arch Surg* **110**, 1501.

Rosenberg C., Tadir Y., Braslavsky D., Fisch B, Karni Z. & Ovadia J. (1990) Endometrial laser ablation in rabbits. a comparative study of three laser types, *Lasers Surg Med* **10** (1), 66–73.

Received 31 July 1991
Accepted 25 October 1991

British Journal of Obstetrics and Gynaecology
January 1992, Vol. 99, pp. 82–83

Haemorrhagic morbidity after diathermy loop excision: effect of multiple pre-treatment variables including time of treatment in relation to menstruation

DAVID LUESLEY
MAHMOOD SHAFI
CATHERINE FINN
JOHN BUXTON

University of Birmingham, Department of Obstetrics and Gynaecology, Dudley Road Hospital, Birmingham

The introduction of loop excision of the cervical transformation zone (Prendiville *et al.* 1989) has enabled more widespread use of treatment at the first visit. Some observers feel that treatment should not be performed at or shortly after menstruation as this might result in excessive bleeding. There are no data relating morbidity to time of treatment in relation to menstruation with any of the commonly used outpatient treatments. To investigate the relation between putative causal variables (including time of treatment in relation to menstruation) and post-treatment morbidity (primary haemorrhage and secondary haemorrhage) we have analysed 197 premenopausal patients treated by diathermy large loop excision of the transformation zone (LLETZ).

Subjects and methods

Treatments were performed by colposcopists trained in the use of LLETZ using a technique described previously (Luesley *et al.* 1990). Intracervical vasoconstrictor was injected in all cases.

The 197 women included in the study were all premenopausal with a cycle length less than 40 days. All have completed 6 months follow-up. The outcome variables analysed were primary haemorrhage (any bleeding interfering with treatment) and secondary haemorrhage. These along with their putative covariates and subcategories are itemized in Table 1.

Continuous data have been categorized by inserting cutpoints to give groups of adequate size for stepwise logistic regression analysis.

Contraceptive methods other than those using steroids or intrauterine devices were classified as non-steroidal, this included those using no contraception. Intrauterine devices were removed at the time of treatment. Otherwise no changes in contraceptive practice were recommended.

Covariates have been analyzed with respect to the two outcomes (primary and secondary haemorrhage) using stepwise logistic regression. This technique allows the introduction of each covariate into the model in a stepwise fashion and a computation of its effect on the outcome in relation to the covariates already in the equation thus the dependance of each covariate on each other and on outcome is assessed. An F to enter value of 4 or more is taken as significant.

Results

When all of the covariates were included in the stepwise logistic regression none was seen to significantly influence the occurrence of primary or secondary haemorrhage.

The categorization of most of the covariates was satisfactory in that no small groups were included.

The time to treat, as expected, was associated with primary haemorrhage as time was one of the covariates used to define primary haemorrhage thus confirming the validity of the model.

Discussion

The advent of simple and safe excisional modes of therapy has

Table 1. Description of all variables and outcome in 197 premenopausal women treated by LLETZ

Variable		*n*	(%)	F to enter or remove 1°Haem*	2°Haem*
Age (years)	<25	59	(30)	0·288	0·007
	25–34	82	(42)		
	≥35	56	(28)		
Parity	Nulliparous	57	(29)	0·27	0·104
	Multiparous	140	(71)		
Lesion Size	≤Three sectors	116	(59)	0·65	0·051
	≥Four sectors	81	(41)		
Depth treated (mm)	≤10	138	(70)	0 028	3.06
	>10	59	(30)		
Time to treat (min)	≤2	60	(30)	16·8**	0 645
	3–4	81	(42)		
	>4	56	(28)		
Day of cycle	1–7	38	(19)	0·124	0·375
	8–14	51	(26)		
	15–21	66	(34)		
	≥22	42	(21)		
Contraception	Steroidal	70	(35)	0·002	0·409
	Non-steroidal	105	(53)		
	IUCD	22	(12)		
1° Haemorrhage	None	127	(64)	N/A	0·023
	Any bleeding	70	(36)		
2° Haemorrhage	No	188	(95)	N/A	N/A
	Yes	9	(5)		

*Stepwise logistical regression using all covariates for specified outcome (primary and secondary haemorrhage).
**Significant.

Correspondence: D. M. Luesley, Senior Lecturer, Department of Obstetrics and Gynaecology, Dudley Road Hospital, Dudley Road, Birmingham B18 7QH.

allowed women to be treated at their first attendance to colposcopy clinics if pre-invasive disease is suspected and the transformation zone fully seen. Some workers are of the opinion that treatment performed at or shortly after menstruation will predispose to haemorrhagic morbidity (Claman & Lee 1974; Rubio *et al.* 1975). Whether or not it is prudent to treat at this time has never been assessed adequately.

We accept that one of the problems of this study was the infrequent occurrence of secondary haemorrhage, one of the outcome measures. We cannot therefore exclude the possibility that this has diminished the sensitivity in detecting small effects. We can, however, feel confident that if there were a clinically significant effect of treating patients in the first 7 days of the cycle then this should have been demonstrated by this study.

The reasons for secondary haemorrhage probably include secondary infection. We do not apply bacteriostatic cream routinely to the treated cervix nor do we routinely prescribe antibiotics following treatment. We believe that the observed infrequent occurrence of possible infection-related morbidity does not justify this approach.

In conclusion, we have been unable to demonstrate any adverse effect in terms of post treatment morbidity in relation to the patient's age, parity, contraceptive method, depth of excision, size of lesion or the day of the cycle on which treatment was performed. There are no grounds for postponing excisional treatment should a patient present in the first week of the menstrual cycle.

References

Claman A. D. & Lee N (1974) Factors that relate to complications of cone biopsy. *Amer J Obstet Gynecol* **120**, 124-128.

Luesley D. M., Cullimore J., Redman C. W E. *et al.* (1990) Loop diathermy excision of the cervical transformation zone in patients with abnormal cervical smears. *Br Med J* **300**, 1690-1693.

Prendiville W., Cullimore J. & Norman S (1989) Large loop excision of the transformation zone (LLETZ). A new method of management for women with cervical intraepithelial neoplasia. *Br J Obstet Gynaecol* **96**, 1054-1060.

Rubio C. A., Thomassen P & Kock Y. (1975) The influence of the size of cone specimens on postoperative morbidity. *Am J Obstet Gynecol* **122**, 939-944.

Received 24 June 1991
Accepted 12 September 1991

British Journal of Obstetrics and Gynaecology
January 1992, Vol. 99, pp. 83–84

The effectiveness of double-gloving in obstetrics and gynaecology

P. M. DOYLE
Registrar

S. ALVI
Medical Student

R. JOHANSON
Senior Registrar

Academic Department of Obstetrics and Gynaecology, Postgraduate School of Medicine, University of Keele, City General Hospital, Stoke on Trent ST4 7LN

There has been much discussion in the medical and non-medical press recently about risks to surgeons of contracting AIDS from infected patients during operative procedures (Sim & Dudley 1988). The discussion has centred mainly on the ethics of screening patients routinely for HIV status pre-operatively. However, pre-operative screening will not detect those individuals who are infected but yet to sero convert. There is reason to believe that the use of 'double-gloving' routinely would considerably reduce the incidence of exposure of the surgeon to patient body fluids (Cole & Gault, 1989; Dodds *et al.* 1990; Geberding *et al* 1990). We report here the result of a prospective randomized controlled trial comparing single with double gloving in obstetric and gynaecological surgery.

Correspondence: Mr P. M. Doyle.

Subjects and methods

Study design

Our null hypothesis was that there was no significant difference between single glove and double gloves in terms of perforation of the inner glove (i.e., the pair next to the skin).

Main outcome measures

The criterion was the proportion of inner glove perforations in the two groups. In addition the number of needle-stick injuries, presence of blood on the skin and subjective views on impairment of dexterity were all recorded.

Power of study and randomization

With 75 participants in each group the power of the study, at $P<0{\cdot}05$, was 80% for detecting a difference of perforations of 15%. Randomization was by sealed envelopes, prepared using random number tables to indicate the use of either one, or two pairs of gloves.

Procedures

Surgeons and their assistants opened sealed envelopes, at the time of operation. Only operative procedures involving use of sharp instruments were included in the trial, thus procedures such as dilatation and curettage or laparoscopy were excluded. At the completion of the operation the gloves were placed in a plastic bag along with a questionnaire which included the following details: Type, duration and blood loss of operation. Grade of staff and contribution to the procedure.

Gloves were tested for perforations using a modified version of the technique described by Cole & Gault (1989). Each glove was filled with approximately 500 ml of water and tested for leaks by gentle manipulation of the water into each digit. Perforations reveal themselves as fine jets of water.

Results

All 150 questionnaires were returned of which 147 were completed correctly and thus usable. The distribution between single/double gloves was 68:79. The trial involved both obstetric and gynaecological operations, the number of patients entered from each was 98 obstetric (of which 79 were caesarean sections) and 49 gynaecological (of which 28 were abdominal hysterectomies).

Our main finding was a highly significant reduction in terms of inner glove perforation (glove next to skin) in the group allocated to double gloves. This was 3 of 79 compared with 24 of 68. Odds ratio was 13·8 (95% CI 3·9–48). It was also found that surgeons perforated their gloves more often than assistants, 33 of 89 compared with 11 of 55. Odds ratio 2·5 (95% CI 1·15–5·5).

There were no significant differences in glove puncture when compared to grade of staff, duration or blood loss of the procedure. This does not agree with the report by Geberding *et al* (1990), but may be due to our small sample size.

It is interesting that there was no difference in the number of outer glove perforations between the single-glove and the double-glove groups (24 of 68 *vs* 21 of 79, respectively). This tends to suggest that whereas a significant number of surgeons, who commented, felt that subjectively their dexterity was impaired by double gloving (46 impaired *vs* 20 not impaired; $P = 0{\cdot}02, \chi^2$) it was not reflected in terms of numbers of perforations. Nor was it reflected in an increase in needle-stick injuries. There were only four of these in the trial of which three occurred in the single glove group.

Discussion

We believe that our study is the first prospective randomized controlled trial comparing single versus double latex gloving, in terms of frequency of glove perforation. The papers referred to in this article are observational studies in the main, except for Sanders *et al.* (1990) who investigated the effectiveness of cloth outer gloves in a randomized prospective trial. However, our observed perforation frequency of the single glove (35%) and outer latex glove (27%) is similar to that observed in the afore mentioned studies, as is the proportion of inner glove perforations in the double glove group (4%).

In conclusion we recommend the routine use of double gloving to all surgeons involved in obstetric or gynaecological surgery. It will reduce the number of occasions when glove perforation will result in potential skin contamination by patient body fluids.

References

Cole R. P. & Gault D. T. (1989) Glove perforation during plastic surgery. *Br J Plas Surg* **42,** 481-483.

Dodds R. D. A., Barker S. G. E., Morgan N. H., Donaldson D R & Thomas M. H. (1990) Self protection in surgery: the use of double gloves *Br J Surg* **77,** 219-220.

Gerberding J. L., Littell C., Tarkington A , Brown A. & Schecter W. (1990) Risk of exposure of surgical personnel to patients' blood during surgery at San Francisco General Hospital. *New Engl J Med* **322,** 1788-1793.

Sanders R., Fortin P, Ross E. & Helfet D (1990) Outer gloves in orthopaedic procedures. *J Bone Joint Surg Inc* **72-A,** 914-915.

Sim A. J. W. & Dudley H. A. F. (1988) Surgeons and HIV. *Br Med J* **296,** 80.

Received 18 March 1991
Accepted 16 September 1991

British Journal of Obstetrics and Gynaecology
January 1992, Vol. 99, pp. 85

CORRESPONDENCE

Stopping smoking—again

Dear Sir,
I read with interest the commentary by Lumley (1991) on stopping smoking. I agree fully that as health workers, we must strive towards a progressive reduction in cigarette smoking in pregnant women. The effect of passive inhalation on the developing fetus is uncertain. However, we know that the effects of passive smoking is around one half to one third that of direct smoking (Hirayoma 1981) and this is likely to contribute to increased nicotine and carbon monoxide levels in the feto-maternal circulation. As such we must also re-educate the women's partners and family members who smoke regarding its deleterious effects on the fetus.

In all cases of stopping an addiction, the person's motivation is of prime importance. I fear that a reduction in fetal birthweight in pregnant women who smoke may not be a strong enough deterrent, especially when smaller babies are often erroneously seen as advantageous and more likely to be successful vaginal deliveries. What is necessary may be more direct aural and visual demonstration of the effect of smoking on the fetus. One interesting study (Kelly *et al.* 1984) showed reduced fetal heart variability and increased fetal heart rate on CTG as well as reduced fetal movements within minutes of smoking. All these improved when the women reduced or stopped smoking. Allowing the woman to see and hear the changes in her fetus's heart rate caused by her smoking provides a much stronger incentive to stop.

Perhaps videotaped evidence of similar trials revealing the direct effects of smoking on the fetus can be shown either at antenatal visits or via the community midwives to the heavier smokers among pregnant women

W. Yoong
The Birmingham & Midland Hospital for Women
Sparkhill
Birmingham

References

Hirayoma T. (1981) Non smoking wives of heavy smokers have a higher risk of lung cancer· a study from Japan. *Br Med J* **282,** 183-185.

Kelly J., Mathews K. A. & O'Conor M. (1984) Smoking in pregnancy· effects on mother and fetus. *Br J Obstet Gynaecol* **91,** 111-117.

Lumley J. (1991) Stopping smoking—again. Commentary *Br J Obstet Gynaecol* **98,** 847-849

British Journal of Obstetrics and Gynaecology
January 1992, Vol 99, pp. 85

First trimester prenatal diagnosis

Dear Sir,
We read with great interest the commentary by Neilson & Gosden (1991) concerning chorion villus sampling (CVS) or amniocentesis for prenatal diagnosis, which echoed the concerns of the MRC Working Party on the Evaluation of Chorion Villus Sampling (1991), that early amniocentesis should only be available within the confines of a randomized trial We fully concur with this opinion and that is why we have been conducting a randomized trial of early amniocentesis and chorion villus sampling at 10–13 weeks gestation, since January 1990. The aim of the trial is to determine the safety and diagnostic accuracy of the two techniques As both techniques are performed in exactly the same way (transabdominal insertion of a 20 gauge needle) by experienced operators, the results will reflect the risks associated with sampling the different tissues rather than differing techniques and wide range of operator experience.

A sample size calculation has illustrated that if the fetal loss rate following CVS is approximately 4%, and the difference between CVS and early amniocentesis is 1%, 6700 patients need to be studied before it can be demonstrated that this difference is significant We have reported the cytogenetic outcome of the first 650 patients (Byrne *et al.* 1991) and established the entry criteria for the trial: (i) a singleton pregnancy from 10–13 weeks gestation with a minimum fetal crown-rump length of 38 mm, and (ii) fetal karyotyping for low risk indications, such as advanced maternal age, family history of chromosomal abnormality (in the absence of balanced parental translocation) and parental anxiety After counselling, patients either choose early amniocentesis or CVS or to be randomized between the two procedures. The procedure related pregnancy loss will not be reported until completion of the trial or if anonymous interim statistical review confirms there to be significant differences that should be made public. Considering the sample size calculation we plan for the trial to become multicentre and are at present accepting applications from other European centres with experience in ultrasound guided invasive techniques and cytogenetic support.

Dominic L. Byrne
Kypros H. Nicolaides
Harris Birthright Research Centre For Fetal Medicine
King's College Hospital
London SE5 9RS

References

Byrne D., Marks K., Azar G. & Nicolaides K. (1991) Randomised study of early amniocentesis versus chorionic villus sampling: a technical and cytogenetic comparison of 650 patients. *J Ultrs Obstet Gynecol* 1(4), 235–240.

MRC Working Party on the Evaluation of Chorion Villus Sampling (1991) Medical Research Council European trial of chorion villus sampling. *Lancet* **337,** 1491–1499.

Neilson J. P. & Gosden C M (1991) First trimester prenatal diagnosis; chorion villus sampling or amniocentesis? *Br J Obstet Gynaecol* **98,** 849–852.

British Journal of Obstetrics and Gynaecology
January 1992, Vol. 99, pp 86–88

BOOK REVIEWS

The Change. Women, Ageing and the Menopause by Germaine Greer Hamish Hamilton, London, 1991, 462 pages, £16.99

The key to Germaine Greer's works is that they all seem to be autobiographical and *The Change* tells us much more about the author's values and her attitudes to men and gynaecologists than about the menopause. Many women will confess that *The Female Eunuch* was one of the most important and influential books that they have ever read and it was a work of great imagination and stature. *Sex and Destiny* was eccentric but worth reading. Sadly these same women 20 years on will feel betrayed by this polemic on the menopause.

Only about a quarter of the book deals with the endocrine problems of the menopause and the treatment with oestrogens and this provides the basis of this review. The rest addresses ageing, the role and achievements of older women, alternative medicine with a detailed section on herbs, and a comprehensive review of literary women and women in literature. There is not a dull page in the whole book but there is a great deal to disagree with.

It is, essentially a hostile, paranoid book blasting vituperative insults at various female politicians, actresses and celebrities, researchers into the menopause—and, incomprehensibly, at one of the most decent and kindly female Fellows of the RCOG. Ms Greer thinks she has the right to be personally and publicly abusive to so many well intentioned people who have merely tried to ensure that women are treated as well as possible

At one level the book is very well researched and it is, therefore, incomprehensible that she comes to the wrong conclusions about oestrogen therapy. She claims not to have come to any conclusion and certainly, her views are muddled, repetitive and eccentric. She is unclear whether women should rejoice at the menopause and become 'crones', or bravely battle through the misery that unjust physiology imposes on them. But the overall message is that a generation of women have been deceived by an unholy alliance of gynaecologists and the pharmaceutical industry.

She mocks the 'Masters of the Menopause' because they do not even know what causes hot flushes or because they do not know how oestrogens improve depression. She must be reminded that vaccination for smallpox was first reported by Edward Jenner in 1798, has been used for two centuries and has eradicated the disease but we are only now understanding its true mechanism of action through advances in modern immunology. The issue is whether oestrogens are effective, whether they are safe, and whether they should be offered to all post-menopausal women, to climacteric women or merely to those with symptoms. The author had a wretched time with her own menopause and describes how oestrogens made her fingers swell to the size of bananas. This is the level of her exaggeration and her anger with gynaecologists. The book is essentially about her own menopause. Much of it is written with great compassion, understanding and humanity but, periodically, she is incapable of resisting a flow of irrational insults directed towards her latest medical victims and their normal practice.

Gynaecologists are attacked because of their views on hysterectomy and she is contemptuous of women, particularly of female doctors and doctors' wives, who willingly submit themselves to such 'mutilation' and 'devastating major surgery'. 'A man who demands that his penis and/or his testicles be cut off will be immediately understood to be deranged; a women who for no good reason wishes to extirpate her uterus will be given every assistance'. It is time to remind our author that the penis is a fairly essential sexual organ for men (and also for women) and men also micturate through it. If a hysterectomy really did also remove the clitoris, vagina and urethra, her comparisons would be valid and the offer of such surgery would have little support. Women are advised to change a male doctor who is doctrinaire for an older female doctor 'who knows what you are talking about'. Perhaps she is right—and for this relief, much thanks.

The book will no doubt be a best-seller, although it does not deserve to be If the public wishes a serious and informed book on the menopause, they can do no better than Wendy Cooper's *No Change* or Barbara Evans's *Life Change*. Even as a book on feminism and man's alleged insensitivity to women it fails because of the exaggerations, the cheap insults, the irrational logic and the clear hatred of doctors. Gynaecologists, particularly male gynaecologists, should be aware of the feminists' contempt of their work but they would be better reading Dr Ann Dally's brilliant history of gynaecology *Women Under The Knife* That is a serious book. Ms Germaine Greer's *The Change* is self-indulgent abusive and overlong.

John Studd

Baillière's Clinical Obstetrics and Gynaecology. International Practice and Research, Vol. 4, No. 3, September 1990, Induction of Ovulation edited by P. G. Crosignani. Baillière Tindall, London, 1990, pages 419–654, Annual subscription £49.00, single issue £22.50

The editorial board of this wide-ranging series has a knack of selecting topical and important subjects for review. This volume, like the others, has contributions from internationally recognised authorities in their field of interest.

The book opens with three chapters dealing with ovulatory disorders that do not require ovarian stimulation: a chapter on body weight (too often ignored as a component of infertility) by the doyenne of this field, Rose Frisch; treatment of hyperprolactinaemia; and glucocorticoid treatment for hyperandrogenism. The major part of the book is concerned with stimulation of ovulation. It begins with an historical and demographic review by Bruno Lunenfeld, which brings home how very recently our drugs in daily use were introduced. Subsequent chapters are divided between treatment *in vivo* and *in vitro*, with the balance inevitably towards the latter, IVF is now the major user of ovulation induction agents.

The volume concludes with a useful chapter on 'Common Problems' and another on hyperstimulation—a timely reminder of an underestimated complication There is a final note on cost-effectiveness of treatment (in which good old clomiphene wins hands down).

There is considerable overlap between chapters concerned with assisted reproduction, and the duplication of material and lack of cross-references suggests little editorial input. There are inevitably some trans-Atlantic differences in viewpoint· non-SI units are used, and to the British reader 'idiopathic glucocorticoid-suppressible hyperandrogenism' sounds an unconvincing form of medispeak. This volume scarcely grapples with the problem of polycystic ovarian disease—the commonest diagnosis in oligomenorrhoeic women—which is touched on in most chapters but merits a review article. There is only a brief mention of multiple pregnancy as a complication of treatment—surely a major omission.

Despite these criticisms, this volume offers a comprehensive review of ovulation induction. It is up-to-date, with inclusion of new dopaminergic drugs, GnRH antagonists and the gonadotrophin-potentiating effect of growth hormone (though there is only a fleeting reference to laparoscopic ovarian cautery). It is also an excellent source of references.

Melanie C. Davies

Baillière's Clinical Obstetrics and Gynaecology. Computing and Decision Support in Obstetrics and Gynaecology, Vol. 4, No. 4, Dec. 1990, edited by R. J. Lilford, Baillière Tindall, London, Philadelphia 1990, pages 656–914, with figures and tables, annual subscription £49.50, single issue £22.50

Many practising clinicians remain bewildered by the micro-chip. Even more horrific, many are being asked to use some form of computer. This volume in the well-known series Clinical Obstetrics and Gynaecology addresses the problem of interfacing clinicians with computers by providing neat introductions of the history and jargon of computing, progressing through current uses to future applications.

For the novice (or those short of time), the first four chapters are essential reading in order to understand what the real computer buffs are doing. The technical aspects of computing and data collection are covered comprehensively in a non-threatening way (and more importantly, interesting to those who would rather steer clear of the subject) Quality data collection and the fact that this is an essential focus for effort is emphasised; there is a refreshing lack of bias, and plenty of sensible advice.

The chapters on computerized automation of clinical trials by Johnson & Lilford and on computer-aided decision support by DeDombal are equally easy on the mind, whilst re-enforcing important principles, and highlighting pitfalls. The computerized analysis of CIG's cardiotocographic records by Maeda makes curiously stimulating reading; it claims that perinatal mortality is reduced by this technique but the number of patients used in the study appears small. It leaves the reader wanting to know what has happened since to their work.

There are a few inaccuracies, for example the Hospital Activity Analysis was discontinued in 1985 The chapter on choosing a computer system might have included 'ergonomics'—the study of the efficiency of persons in their working environment in order to reduce the chance of back or eye strain or carpel tunnel problems—aspects of health and safety that will become law next year

Most of the remainder of the book is dedicated to 'expert systems' and decision analysis, which although intellectually stimulating, leave one wondering how they would be accepted into clinical practice. Large assumptions are made in the assigning of probability to conditions and complications, and the casual reader might be easily lost, but this does represent a comprehensive account of a subject likely to become increasingly important.

The opportunity to emphasise the good that computers can play in helping with personal and local audit is passed over in favour of their value in administration, reflecting a personal view rather than that prevailing. Indeed, it could be local audit that might provide the data to allow application of decision analysis to a specific hospital population.

Overall, an important reference for a hospital library, covering most aspects and principals of clinical computing in obstetrics and gynaecology To their credit, the individual chapters discuss the limitations and deficiencies of each topic and aid selective reading by having a stated summary and conclusion.

Philip J. Banfield

Homebirth and Other Alternatives to Hospital by Sheila Kitzinger Dorling Kindersley, London, 1991, 208 pages, £12

The jacket cover is authoratative 'A source of wise counsel and support for every woman who is considering her options in childbirth'. Actually this is a book for women who have already considered, decided—and booked the birth pool to boot,—and probably all prior to conception The book has a chapter headed 'What's wrong with hospitals' that merely serves to reinforce the reader's conviction that you can't possibly have an orgasmic birth in hospital. Orgasmic? Yes, all Kitzinger homebirths are orgasmic experiences. They are also very pretty (there are lots of nice grainy black and white pictures of homebirth by the talented photographer, Marcia May)

Varying amounts of attention are given to the three major problems of homebirth. How to get one in the first place can be a major obstacle. Sheila Kitzinger suggests standing in front of a mirror and practising saying 'I want a home birth', prior to seeing a doctor. She is actually very clear and concise on the subject of calculating risk but does seem to offer homebirth as a panacea for almost every problem in the obstetric handbook She says almost nothing about the after-effects of childbirth, in terms of the mess, gore and gunge, apart from a reference to the need for a sieve (to collect the bits in the birth pool). Finally, there is nothing at all about how to cope with an emergency transfer to hospital. This is a major omission. If you are going to have a homebirth, you need to be prepared for all eventualities, as you do for a hospital birth. An emergency transfer is a possibility, albeit a rare one and it is important to know that if this happens, it in no way denotes a failure on the mother's or carer's part—it is simply the course that some pregnancies will inevitably follow. Quite definitely, a coffee table birth book—all sweetness, light and orgasm.

Vivienne Parry

Year Book of Neonatal and Perinatal Medicine 1990 edited by Marshal H. Klaus & Avroy A. Fanaroff Mosby Year Book, St Louis, Baltimore, London, 342 pages with figures and tables, £41.00

Like many obstetricians I have nearly always regarded passing the baby to paediatric jurisdiction as a scrum-half activity. Once the 'ball' is out then my responsibilities are taken over by other 'players'.

However, on reading this volume (and I have not previously dipped into its predecessors), I realized how much our two disciplines are being intertwined. Although many of the papers reported on are essentially for paediatric consumption, there are many gems that could excite accoucheurs. It has been over 20 years since Miller and Littlepage showed that smoking women rarely breast fed their babies; it is not until reading page 212 in 1991 where it is described that the inhaled products of cigarettes appear concentrated in breast milk that one realises that avoidance of breast feeding by smoking mothers is, unknown previously to them, a sensible step to take.

The format of Year Books is maintained in this edition. There is a succinct precis of the paper, followed often by an apposite quotation and then a critique by an 'expert' in the subject. These quotations such as 'When you have nothing to say, say nothing—Charles Caleb Colton' add piquancy to the reviews that follow each summary of the paper The selections of papers are wide, interesting and collected together in loosely similar subjects. There is an excellent up-to-date review of Jaundice in the Newborn followed by chapters on the Fetus and Genetics In Medical Complications of Pregnancy one is again reminded that prior to pregnancy, use of barrier contraceptives increases the risks of pre-eclampsia. I wonder if the London Rubber Co. know this? Also the dangers to the fetus of drug-taking are further emphasised making us hope that the US level of drug addiction will never reach such epidemic proportions in the UK.

Like its sister volumes this edition should be dipped into by all obstetricians if only to allow them to startle their paediatric colleagues with their depth of knowledge

Finally in the introduction on page xii is the word 'maven'—this is not in my OED. Can anyone tell me what it means or is it the only misprint in this book?

John McGarry

Drugs in Pregnancy and Childbirth by Judy Priest. Pandora Press, London, 1990, 224 pages with figures and tables, £5.99

This paperback is by a wife and mother who trained as an anthropologist and a nurse and now trains antenatal teachers for the National Childbirth Trust. I opened it expecting to find some combination of the incorrect deductions and statements which are quoted from textbook to textbook by professional 'experts' in the field, the media-type exaggerations of risks and the unsupported and ill-balanced nonsense of the health educationists and 'do-gooders' Instead, I found by far the best informed and best balanced account of the problems of drugs in pregnancy I have yet to read in professional or lay literature

There is real understanding here of the balance between the very small risks of drug treatment in pregnancy and therapeutic need, put in a way that patients and even doctors may understand. The preconception approach to management of drugs in pregnancy is rightly stressed. The Debendox story is explained and the myth that sulphonamides are harmful in pregnancy ignored. The point is made that while smoking is undesirable in or out of pregnancy, the great majority of women who find it difficult to give up even heavy smoking will have normal babies. The fantasy that an alcoholic drink of an evening will harm the baby is dismissed With respect to the use of drugs in labour, both oxytocics and analgesics, the balance of arguments for and against is explained with great care and understanding for every agent in use. The emphasis throughout is to tell the patient the truth, rather than the exaggerated prejudices of the teller, and to let her have a say in the decisions wherever possible. On the other hand great care is taken not to pre-empt real clinical decisions With respect to choice of anticoagulants—'This is a matter of clinical judgement and you need to find out what your doctor recommends and the grounds for his or her belief'.

I can only congratulate the author on more understanding of the subject than most doctors, on a better balance and perspective that most clinical pharmacologists, obstetricians and paediatricians, and on an excellent production. The book should be highly recommended to all women considering embarking on a pregnancy and all those in need of medication during a pregnancy. In my view it should be compulsory reading for medical students and considered as an important volume for doctors specialising in obstetrics.

Denis Hawkins

Books received some of which may be reviewed at a later date

Maternal Mortality. A Global Factbook compiled by C. Abou Zahr & E. Royston World Health Organization, Geneva, 1991, 608 pages, Sw.fr.50.00, US$45.00 (Sw.fr.35 00 in developing countries).

Introduction to Sterilization, Disinfection and Infection Control second edition by Joan Gardner & Margaret M. Peel. Churchill Livingstone, Edinburgh, 1991, 272 pages illustrated, £24.95

British Postgraduate Medical Federation. Patterns of Medical Staffing by Robin Dowie. Series commissioned by the Department of Health, HMSO 1991. **Overview,** 42 pages £5.60 **Obstetrics and Gynaecology,** 115 pages, £12 95. **Paediatrics,** 83 pages £10.00.

Taking it Lying Down. Sexuality and Teenage Motherhood by Frances Hudson & Bernard Ineichen. Macmillan, 1991, 234 pages, £30.00

The Stress of Multiple Births edited by David Harvey & Elizabeth Bryan Available from Multiple Birth Foundation, Queen Charlotte's and Chelsea Hospital, Goldhawk Road, London W6 0XG, 140 pages, illustrated, £15.00 (£12.00 to members of MBF)

Practical Mother and Child Health in Developing Countries 4th edition by G. J Ebrahim. Macmillan Education Ltd, Basingstoke, London 1991, 153 pages, £9.99

Lecture Notes on Clinical Investigation edited by Derek Maclean, Malcolm Bateson & Christopher Pennington. Blackwell Scientific Publications Ltd, Oxford, 1991, 229 pages with figures and tables, £11.95

Living in the Real World. Families Speak about Down's Syndrome edited by C. F. Goddey Twenty-One Press, 1991, 135 pages. Available from Newham Parents' Centre Education Bookshop, 745 Barking Road, London E13 9ER. £6.00

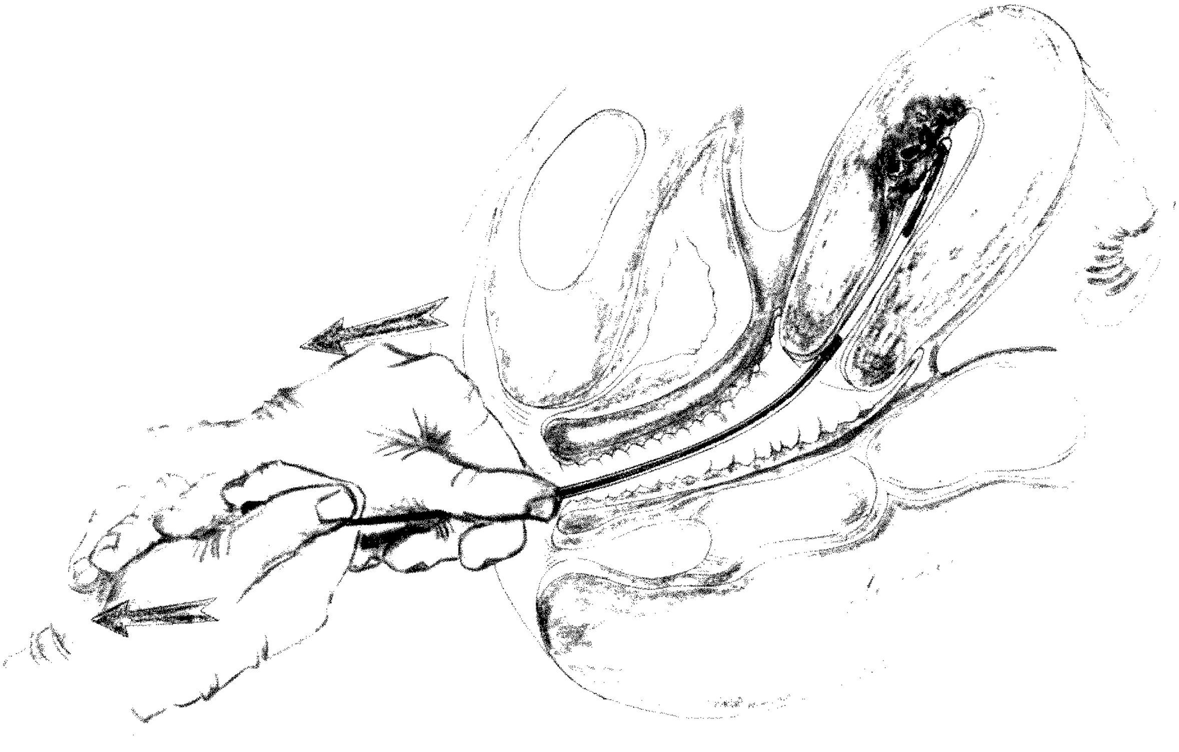
Proceedings and Symposiums

Genetics, Ethics and Human Values. Human Genome Mapping, Genetic Screening and Gene Therapy. Proceedings of the XXIVth CIOMS Round Table Conference held in Japan, 1990, edited by Z. Bankowski & A. M. Capron, WHO, Geneva 1991, 200 pages Sw.fr.20.00 US$18.00 (Sw.fr.14.00 in developing countries)

PIPELLE DE CORNIER

A DISPOSABLE, ENDOMETRIAL SUCTION CURETTE FOR HISTOLOGIC BIOPSY OF THE UTERINE MUCOSAL LINING OR SAMPLE EXTRACTION OF UTERINE MENSTRUAL CONTENT.

- *Histologic specimen*
- *Liberal quantity*
- *Simple technique*
- *Patient acceptable*
- *Economic cost*



With just one use, the advantages of the unassuming looking PIPELLE DE CORNIER become immediately apparent. The technique is simple and takes only seconds. The patient is comfortable and, with rare exception, experiences no pain. There are no hook-ups to perform, insertion is easy and there's no disquieting noise. The resultant specimen is liberal in quantity, histologic in quality and protected from contamination by foreign cells that can hinder interpretation. Cost conscious pricing fits any private practice budget and allows routine use of the PIPELLE DE CORNIER. Try it just once. Experience for yourself the convenience and effectiveness of this exceptional instrument.

Distributed by:

EURO SURGICAL LIMITED
The Common, Cranleigh, GU6 8LU, U.K.
Telephone: 0483 267363 Fax: 0483 267281

Please send me more information on the Pipelle
Name
Title
Address

Telephone

British Journal of Obstetrics and Gynaecology

Volume 99 No 1 January 1992

CONTENTS

Commentaries

The British Journal of Obstetrics and Gynaecology—1992 1
D. B. Paintin

Prognosis of surviving very low birthweight infants: still in the dark 1
G. J. Escobar

MD madness 3
J. Studd

Obstetrics

Randomized trial of amniotomy in labour versus the intention to leave membranes intact until the second stage 5
J. F. Barrett, J. Savage, K. Phillips & R. J. Lilford

Changes in decidual stromal cell function associated with labour 10
H. Khan, O. Ishihara, M. H. F. Sullivan & M. G. Elder

Does admission to hospital for bed rest prevent disease progression or improve fetal outcome in pregnancy complicated by non-proteinuric hypertension? 13
C. A. Crowther, A. M. Bouwmeester & H. M. Ashurst

Fetal and Neonatal Medicine

Normal amniotic pressure throughout gestation 18
N. M. Fisk, D. Ronderos-Dumit, Y. Tannirandorn, U. Nicolini, D. Talbert & C. H. Rodeck

Folate and vitamin B_{12} concentrations in maternal and fetal blood, and amniotic fluid in second trimester pregnancies complicated by neural tube defects 23
D. L. Economides, J. Ferguson, I. Z. Mackenzie, J. Darley, I. I. Ware & M. Holmes-Siedle

Fetal acidaemia, the cardiotocograph and the T/QRS ratio of the fetal ECG in labour 26
N. A. Maclachlan, J. A. D. Spencer, K. Harding & S. Arulkumaran

Clinical assessment of fetal electrocardiogram monitoring in labour 32
K. W. Murphy, V. Russell, P. Johnson & J. Valente

Transvaginal sonography for fetal measurement in early pregnancy 38
A. Kustermann, A. Zorzoli, D. Spagnolo & U. Nicolini

In-utero sound levels when vibroacoustic stimulation is applied to the maternal abdomen: an assessment of the possibility of cochlea damage in the fetus 43
S. Arulkumaran, D. Talbert, T. S. Hsu, S. Chua, C. Anandakumar & S. S. Ratnam

Fetal urine biochemistry: an index of renal maturation and dysfunction 46
U. Nicolini, N. M. Fisk, C. H. Rodeck & J. Beacham

Maternal serum unconjugated oestriol and human chorionic gonadotrophin levels in pregnancies with insulin-dependent diabetes: implications for screening for Down's syndrome 51
N. J. Wald, H. S. Cuckle, J. W. Densem & R. B. Stone

Gynaecology

Is Stage I epithelial ovarian cancer overtreated both surgically and systemically? Results of a five-year cancer registry review 54
C. B. Finn, D. M. Luesley, E. J. Buxton, G. R. Blackledge, K. Kelly, J. A. Dunn & S. Wilson

A randomized clinical trial on the benefit of adhesiolysis in patients with intraperitoneal adhesions and chronic pelvic pain 59
A. A. W. Peters, G. C. M. Trimbos-Kemper, C. Admiraal, J. B. Trimbos & J. Hermans

Diagnosis of bacterial vaginosis in a gynaecology clinic 63
P. E. Hay, D. Taylor-Robinson & R. F. Lamont

Reproductive Science

Intergenerational studies of human birthweight from the 1958 birth cohort. 1. Evidence for a multigenerational effect 67
I. Emanuel, H. Filakti, E. Alberman & S. J. W. Evans

Case Reports

Prospective modulation of platelet function and volumes by aspirin and dipyridamole in an at-risk pregnancy 75
M. H. F. Sullivan, L. Fusi, J. Brosens & M. G. Elder

Severe non-diabetic keto-acidosis causing intrauterine death 77
J. M. Land, C. H. D. A'Court, M. D. G. Gillmer & J. G. G. Ledingham

Pregnancy complicated by Charcot-Marie-Tooth disease, requiring intermittent ventilation 79
D. L. Byrne, O. A. Chappatte, G. T. Spencer & K. S. Raju

Short Communications

Transilluminating ureteric stents for preventing operative ureteric damage 81
J. H. Phipps & N. J. Tyrrell

Haemorrhagic morbidity after diathermy loop excision: effect of multiple pre-treatment variables including time of treatment in relation to menstruation 82
D. Luesley, M. Shafi, C. Finn & J. Buxton

The effectiveness of double-gloving in obstetrics and gynaecology 83
P. M. Doyle, S. Alvi & R. Johanson

Correspondence

Stopping smoking—again 85
W. Young

First trimester prenatal diagnosis 85
D. L. Byrne & K. H. Nicolaides

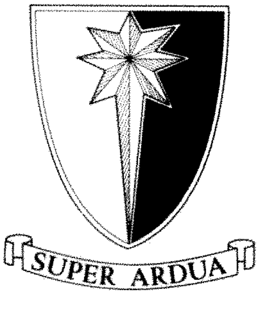
Book Reviews 86

Blackwell Scientific Publications
OXFORD · LONDON · EDINBURGH · BOSTON · MELBOURNE · PARIS · BERLIN · VIENNA
Printed in Great Britain by Headley Brothers Ltd The Invicta Press Ashford Kent and London

Volume 99, Number 2, February 1992 BJOGAS 99(2) 89–174 1992 ISSN 0306-5456

British Journal of Obstetrics and Gynaecology

Edited by David B. Paintin



Published on behalf of the
Royal College of Obstetricians and Gynaecologists
by Blackwell Scientific Publications

6 reasons why more doctors prescribe Prempak-C and Premarin than any other HRT.

50 YEARS EXPERIENCE

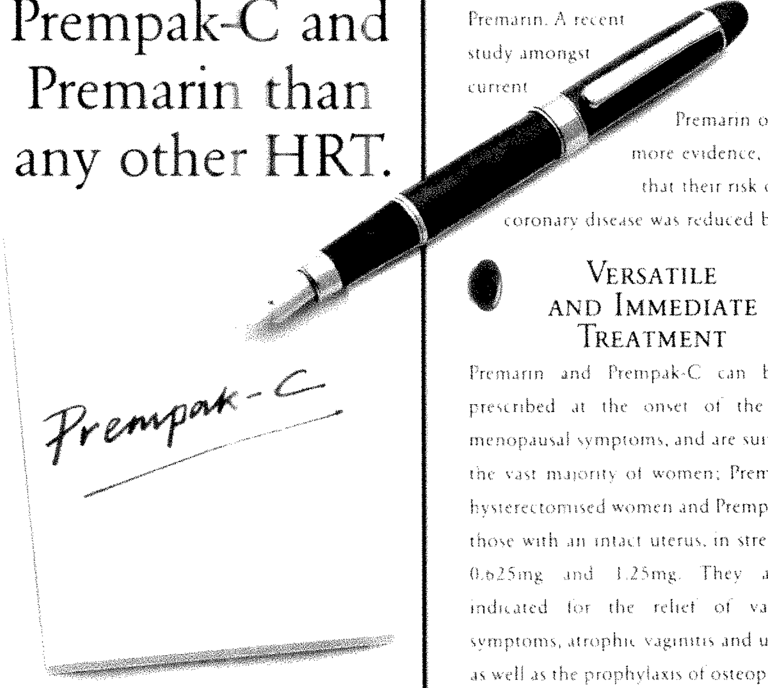
Premarin, a natural conjugated oestrogen, which is also used in the formulation of Prempak-C, is the only oestrogen used in any HRT with 50 years experience. The majority of long term studies, therefore, relate to the conjugated oestrogen found only in these products.

LONG TERM SAFETY - BREAST CANCER?

Both doctors and patients are justifiably concerned about the potential risks of breast cancer for women taking HRT. Whilst there is suggestive evidence of a small increased risk of breast cancer with long-term HRT (greater than 5 years), this varies with the type and dose of the oestrogen used. However, a recent comprehensive review of 31 studies provides evidence that menopausal therapy consisting of 0.625mg/day of conjugated oestrogens does not increase the risk of breast cancer.[1] Most studies, in fact, relate to conjugated oestrogen and so there is insufficient data to arrive at similar conclusions for any other regimen.

PROPHYLAXIS OF OSTEOPOROSIS

Prempak-C and Premarin are both indicated for the prophylaxis of osteoporosis. A minimum daily dose of 0.625mg Premarin preserves bone mass, therefore reducing the risk of debilitating injuries such as hipfractures, by up to 66%.[2,3] Further estimates suggest that prescribing Premarin for at least 10 years will reduce the risk of mortality linked to osteoporosis by 60%[4]



REDUCING CARDIOVASCULAR DISEASE RISKS

A recent review of considerable epidemiological evidence has shown, overall, a 50% reduction in risk of coronary disease in oestrogen users.[5] The most common form of oestrogen used in all these studies was conjugated oestrogen, ie Premarin. A recent study amongst current users of Premarin offers yet more evidence, showing that their risk of major coronary disease was reduced by 60%.[6]

VERSATILE AND IMMEDIATE TREATMENT

Premarin and Prempak-C can both be prescribed at the onset of the earliest menopausal symptoms, and are suitable for the vast majority of women; Premarin for hysterectomised women and Prempak-C for those with an intact uterus, in strengths of 0.625mg and 1.25mg. They are also indicated for the relief of vasomotor symptoms, atrophic vaginitis and urethritis, as well as the prophylaxis of osteoporosis in women at risk.

COST EFFECTIVE

Treatment costs are becoming increasingly important, especially as long term therapy can last from 5 to 10 years or longer. Compared to other forms of HRT, Wyeth's products cost remarkably little; Premarin costs just £1.65 and Prempak-C costs £3.98, for 28 days of therapy.[7]

PREMPAK-C
PREMARIN

ABBREVIATED PRESCRIBING INFORMATION

PREMARIN **USES:** Menopausal and post menopausal oestrogen therapy in women without a uterus for vasomotor symptoms, allied disorders such as atrophic vaginitis, kraurosis vulvae, atrophic urethritis, and prophylaxis of osteoporosis in women at risk of developing fractures.
DOSAGE AND ADMINISTRATION: Natural conjugated oestrogens 0.625mg - 1.25mg daily. Continuous administration is recommended. In women with an intact uterus the addition of a progestogen for 10-12 days per cycle is essential.
CONTRA-INDICATIONS: Known or suspected pregnancy and during lactation. History of known or suspected cancer of the breast. Oestrogen dependent neoplasia. Undiagnosed abnormal genital bleeding. Active thrombophlebitis or thromboembolic disorders. Acute or chronic liver disease. Rotor or Dubin-Johnson syndrome. Severe cardiac or renal disease.
WARNINGS AND PRECAUTIONS: Some studies have reported a small increased risk of breast cancer in long term oestrogen replacement therapy users (greater than 5 years), others however have not shown this relationship. It is not known whether concurrent progestogen influences this risk. The risk of endometrial hyperplasia and carcinoma with unopposed oestrogen use is lowered by the addition of a progestogen. Diseases that may deteriorate during therapy include otosclerosis, multiple sclerosis, systemic lupus erythematosis, porphyria, melanoma, epilepsy, migraine and asthma. Use with caution in patients with pre-existing uterine fibroids, endometriosis, breast nodules, fibrocystic disease, and in those with a history of deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction, cardiac or renal dysfunction. Discontinue if jaundice, migraine, visual disturbances, thromboembolic phenomena or significant hypertension develop. Certain endocrine and liver function tests may be affected. Rarely idiosyncratic hypertension may occur. Discontinue treatment prior to surgery or prolonged immobilisation. Gallbladder disease. Insulin requirements may be altered. Premarin is not an oral contraceptive.
SIDE EFFECTS: The following have been reported with oestrogen therapy: premenstrual like syndrome, increase in size of uterine fibromyomata, vaginal candidiasis, changes in cervical erosion and secretion, cystitis like syndrome, breast changes, gastrointestinal symptoms, chloasma, melasma, erythema multiforme, erythema nodosum, haemorrhagic eruption, alopecia, hirsutism, steepening of corneal curvature, intolerance to contact lenses, headaches, migraine, dizziness, mental depression, chorea, weight changes, reduced carbohydrate tolerance, aggravation of porphyria, oedema, changes in libido, leg cramps.
PRODUCT LICENCE NUMBERS: Premarin 0.625mg PL0011/0165 Premarin 1.25mg PL0011/0166 Premarin 2.5mg PL0011/0167. **BASIC NHS PRICE:** Premarin 0.625mg £1.65 (28 days). For full prescribing information please refer to data sheet.

PREMPAK-C **USES:** Menopausal and postmenopausal oestrogen therapy for women with an intact uterus for vasomotor symptoms, allied disorders such as atrophic vaginitis, kraurosis vulvae, atrophic urethritis, and prophylaxis of osteoporosis in women at risk of developing fractures.
DOSAGE AND ADMINISTRATION: Natural conjugated oestrogens 0.625mg - 1.25mg daily and one norgestrel 0.15mg tablet should be taken daily from day 17 to day 28 of oestrogen therapy.
CONTRA-INDICATIONS: As for Premarin.
WARNINGS AND PRECAUTIONS: As for Premarin. Prempak-C is not an oral contraceptive.
SIDE EFFECTS: As for Premarin. Breakthrough bleeding and spotting. Change in menstrual flow, dysmenorrhoea, amenorrhoea.
PRODUCT LICENCE NUMBERS: Prempak-C 0.625mg PL0011/0161 Prempak-C 1.25mg PL0011/0162. **BASIC NHS PRICE:** £3.98 - 28 days. For full prescribing information please refer to data sheet.
REFERENCES 1 Dupont W.D and Page D.L. (1991) Arch. Int. Med. 151, 67-72. 2 Lindsay R. et al. (1984) Obstet. Gynecol. 63, 759-763. 3 Kiel D.P. et al (1987) NEJM, 317, 1169-1174. 4 Ross R.K. et al. ([illegible]) Lancet, I, 505. 5 Stampfer M.J. and Colditz G.A. (1991) Prev. Med, 20, 47-63. 6 Stampfer M.J. et al (1991) NEJM, 325, 756-762. 7 MIMs February 1992. *Trademark
Wyeth Laboratories, Huntercombe Lane South, Taplow, Maidenhead, Berkshire SL6 0PH.

British Journal of Obstetrics and Gynaecology

Editor: David B. Paintin
Editorial Advisers: F. E. Hytten *London*, I. Chalmers *Oxford*
Assistant editors: Sheila L. B. Duncan *Sheffield*, R. P. Husemeyer *Grantham*
Editorial assistants: Sonja Chayen, Valerie Bolton, Jayne Marchant
Statistical advisers: D. G. Altman *London*, Diana Elbourne *Oxford*, Helen Tate *Saffron Walden*

Editorial board
C.H. Buckley *Manchester*
R.W.I. Cooke *Liverpool*
J.O. Drife *Leeds*
I.D. Duncan *Dundee*
S. Franks *London*
R.B. Fraser *Sheffield*
J.M. Grant *Bellshill*
J.M. McGarry *Barnstaple*
J.P. Neilson *Edinburgh*
R.S. Sawers *Birmingham*
G.E. Smart *Edinburgh*
P.J. Steer *London*
J.W.W. Studd *London*
M. de Swiet *London*
D.W. Warrell *Manchester*

British Journal of Obstetrics and Gynaecology is published on behalf of the Royal College of Obstetricians and Gynaecologists by Blackwell Scientific Publications. The *Journal* publishes reports of original work in obstetrics and gynaecology and related subjects such as human reproductive physiology and contraception; articles reviewing topics in these fields are also acceptable. A section for brief communications, including case reports, allows more rapid publication of papers of not more than 600 words. *British Journal of Obstetrics and Gynaecology* is covered in *Current Contents, ISI/BIOMED, Science Citation Index, Index Medicus, CABS*, and the ADONIS service, whereby copies of individual articles can be printed out from compact disks (CD-ROM) on demand. An explanatory leaflet is available from the publisher.

Books for review

Books for review should be sent to the *British Journal of Obstetrics and Gynaecology*, 27 Sussex Place, Regent's Park, London NW1 4RG.

Correspondence

Letters should be sent to The Editor, *British Journal of Obstetrics and Gynaecology*, 27 Sussex Place, Regent's Park, London NW1 4RG.

As the space available for correspondence is limited, only a selection of letters submitted will be printed. Letters should be brief, factual and related to original work recently published in the *Journal* The editorial staff reserve the right to shorten letters and make minor corrections. Letters may be published together with a reply from the original author.

Subscription information

The *British Journal of Obstetrics and Gynaecology* is published monthly and annual subscriptions for 1992, accepted on a calendar year basis only, are £90.00 (UK), $165.00 (USA and Canada) and £95.00 (elsewhere), post free. Fellows, Members and successful Part 1 candidates of the Royal College of Obstetricians and Gynaecologists are entitled to subscribe at the special price of £29.00 (UK), £39.00 elsewhere and $68.00, USA and Canada (add $4.76 GST in Canada), also post free. Orders for current subscriptions and back issues should be sent to Blackwell Scientific Publications Ltd, PO Box 88, Oxford OX2 0NE; all other business correspondence, including orders for offprints and advertising space, should be addressed to Blackwell Scientific Publications Ltd, Osney Mead, Oxford OX2 0EL (telephone no. 0865 240201, telex 83355 Medbok G, fax 0865 721205).

Dispatch

The *Journal* is dispatched within Europe by surface mail, to other continents by various forms of air speeded delivery: to the US* by air freight for forwarding by second class post, to India by air freight for guaranteed local delivery, and to all other countries by Accelerated Surface Post.

Copyright and photocopying

Articles published in the *Journal* become its copyright. Reproduction elsewhere, in whole or in part, is not permitted without the previous written consent of the author and editor, and the customary acknowledgments must be made.

© 1992 Blackwell Scientific Publications Ltd. Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by Blackwell Scientific Publications Ltd for libraries and other users registered with the Copyright Clearance Center (CCC) Transactional Reporting Service, provided that the base fee of $06.00 per copy is paid directly to CCC, 27 Congress Street, Salem, MA 01970, USA. 0306-5456/92 $06.00.

This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale. Special requests should be sent to the Editor.

Business correspondence

Orders and remittances relating to subscriptions, back numbers and offprints should be sent to Blackwell Scientific Publications, PO Box 88, Oxford.

Advertisements

Advertisement bookings and enquiries should be sent to the Advertisement Manager, Blackwell Scientific Publications, Osney Mead, Oxford OX2 0EL (Telephone 0865 240201, Fax 0865 721205).

This journal is printed on acid-free paper.

---

* *Postmaster, send address changes to* British Journal of Obstetrics and Gynaecology, *c/o Mercury Airfreight International Ltd., 2323 EF Randolph Avenue, Avenal NJ07001 (US Mailing Agent). Second Class Postage Paid at Rahway NJ.*

Directions to contributors

All papers should be sent to The Editor, *British Journal of Obstetrics and Gynaecology*, 27 Sussex Place, Regent's Park, London NW1 4RG. Papers received and the data they contain are assumed to have been submitted exclusively to the *British Journal of Obstetrics and Gynaecology* and *all* authors must give signed consent to publication in a letter sent with the manuscript. The Editor will decide on the time of publication and retains the usual right to modify the style and length of a contribution; major changes will be agreed with the author(s).

Peer review
Manuscripts are subjected to peer review in relation to both the scientific and the statistical content. As far as possible the scientific referees are unaware of the authorship and the department of origin of the work. The peer review process takes a minimum of six weeks. Papers that are accepted are published about four to five months later.

Presentation of manuscripts
Three copies of the manuscript and illustrations should be sent Manuscripts should be typed double spaced on one side of the paper, with wide margins. To facilitate blind refereeing, the names of the author(s), their appointment(s) and their department(s) should be given on a separate front sheet and any acknowledgments on a separate back sheet. As far as possible, authors should avoid identifying themselves or their department in the text, but such identification is inevitable in some types of paper. When papers have been accepted for publication, and after any revision has been completed, authors are encouraged to submit the final version on disk. This should be IBM compatible. An accurate hard copy must accompany each disk, together with details of the type of computer used, the wordprocessing software and the disk operating system. The text must not be justified. Particular attention should be taken that the final version adheres to the style of the journal in all respects Further details can be obtained from the publishers. Authors are advised to keep a copy of all manuscripts, as no responsibility can be accepted for loss.

Reports of original work should usually be arranged in the conventional order of abstract, introduction, methods, results, discussion, acknowledgments and references, with suitable headings for each part. Two further sub-divisions, with appropriately less significant headings, can be used; the third order heading runs on with text at a paragraph opening. Results may be presented in the text, in tables and/or figures, but the text should, in general, comment on rather than repeat information in tables. Abstracts are structured and use an appropriate selection of the headings: Objective; Design; Setting; Subjects; Interventions, Main outcome measures; Results; Conclusions. Abstracts should not exceed 250 words.

Case reports and short communications do not require a summary or introduction. Short communications should not exceed 600 words and contain no more than one table or figure.

Letters to the editor are published only if they comment usefully on material published in previous issues. Letters should not exceed 400 words and must be typed with double line-spacing.

Tables and figures
Tables and figures should be separate from the text, with their positions indicated in the text margin. Both are numbered with arabic numerals. Coloured illustrations are used sparingly when these appreciably improve clarity

Figures should be marked on the back (lightly in pencil) only with the name of the paper, the figure number and to indicate the top Each should have a descriptive legend typed on a sheet separate from the figure. Photographs should be unmounted glossy bromide prints of good contrast

Figures consist of all material which cannot be set in type, such as photographs, line drawings, etc. Tables are not included in this classification and should not be submitted as photographs Original X-ray films should not be sent—glossy prints must be submitted.

Line drawings should be on white board, arranged to conserve space, and should allow for reduction to 81 mm (single column) or 170 mm (double column). Computer-generated graphics should be printed on good quality plain white paper The layout should be as simple as possible—three-dimensional effects should be used only if this is necessary to express a third variable.

Typewritten lettering should not be used on illustrations and explanations should appear in the legend not on the figure itself

Unless written permission for publication from the patient, or the parent or guardian is submitted, the identity of patients in illustrations should be completely concealed by restricting the field to the area of interest or by obscuring the face.

Units and abbreviations
Measurements should be expressed in SI units with the exception of haemoglobin (g/dl) and blood pressure (mmHg). If the original observations were recorded in other units this should be stated, together with the appropriate conversion factors. Standard abbreviations, without punctuation, are used *Units, Symbols and Abbreviations* (1988) published by the Royal Society of Medicine provides a useful guide. Abbreviations are used sparingly and only if a lengthy name or expression is repeated frequently throughout the manuscript. Words must appear in full on first appearance in both abstract and text, followed by the abbreviation in parenthesis.

Drugs are described by their official names but trade names should be indicated in brackets the first time a drug is quoted in the main text.

Statistics
Authors should describe clearly the design of their investigation and the source of the data. All statistical methods should be specified so that it is clear which was used where Papers omitting this information may be returned without review. The basic principle to follow is to supply sufficient information about the design and methods of analysis to allow the research to be repeated by someone else.

The journal has published check lists to guide contributors preparing accounts of certain types of research. These appeared in 1989 (Vol **96**): Bracken M. B., Reporting observational studies, 383–388; Wald N. & Cuckle H , Reporting the assessment of screening and diagnostic tests, 389–396; Grant A., Reporting controlled trials, 397–400.

Some points of detail to note are:

(1) It is not acceptable to present the results of a statistical analysis solely by a *P* value—actual results such as means or proportions should always be given, along with the test statistic.
(2) The use of confidence intervals is encouraged.
(3) The symbol ± should not be used when presenting SE or SD. Presentation such as 'the mean . . . was 14·2 (SD 3·2) mg' is preferred.
(4) When paired comparisons are made it is desirable to indicate the variability of within-pair differences.
(5) Unusual methods of analysis should be described and/or referenced.

Authors are referred to the general statistical guidelines of Altman *et al.* (1983) for advice about the presentation and interpretation of the statistical aspects of their research.

Altman, D. G., Gore. S M., Gardner, M. J & Pocock, S. J. (1983) Statistical guidelines for contributors to medical journals. *Br Med J* **286**, 1489–1493.

Human experiments
Manuscripts should contain a statement that the work was approved by the ethics committee of the institution in which it was done and that subjects gave informed consent to the work The editors reserve the right to reject papers if they consider the ethical justification to be questionable.

References
In the text, use the name of the author(s) followed by their date of publication; where there are two authors use the form: Smith & Brown 1972; where there are more than two authors use Robinson *et al* 1979.

Arrange the list of authors quoted at the end of the text in alphabetical order set out as follows·

Name(s) and initials of all author(s), year of publication (in brackets), title of the article, name of the journal (abbreviated according to *Index Medicus*), volume number, first and last page numbers In the case of books the order is· Name(s) and initials of author(s), year of publication (in brackets), full title, edition, publisher and place of publisher, page numbers. Where appropriate, the chapter title and the names of the editors should be given.

References to 'personal communications' and 'unpublished work' may be quoted in the text but should not be included in the references Examples of the style to be used are given below.

Trudinger B J., Lewis P. J. & Petit B. (1979) Fetal breathing in intrauterine growth retardation. *Br J Obstet Gynaecol* **86**, 432-436

Hytten F. E. & Leitch I (1971) *The Physiology of Human Pregnancy* 2nd edn, Blackwell Scientific Publications, Oxford, p 26.

Proofs and offprints
Manuscripts should specify the name and address of the author to whom correspondence and page proofs should be sent Only essential corrections can be accepted, more extensive alterations, which may delay publication, will be charged to the author. Fifty offprints of each paper are supplied free, but additional copies may be ordered on the printed sheet sent with the proofs.

British Journal of Obstetrics and Gynaecology
February 1992, Vol. 99, pp. 89–95

COMMENTARIES

The dangers of intra-amniotic methylene blue

Invasive procedures have acceptable, and usually accepted, risks for the fetus. Trauma to the fetus or placenta, miscarriage or preterm labour, or neonatal problems: all are recognized hazards. These risks are reduced by the skill of experienced operators using ultrasound. There is, however, another risk—that of the wrong diagnosis: maternal tissue mistakenly thought to be fetal, or inadvertent sampling of the same twin twice. It may be impossible to differentiate easily between maternal and fetal tissue, but improving ultrasound technology has simplifited the differentiation between one twin's sac and the other. This was not always so and frequently methylene blue was instilled into the first sac sampled so that a second sample from the same sac could be identified by the blue colour of the amniotic fluid. An apparently safe drug when used therapeutically and diagnostically, the only disadvantage associated with methylene blue appeared to be in the third trimester when it was used to diagnose ruptured membranes. The baby born soon after the instillation of the dye might be stained so blue to the distress of the mother and interfering with the clinical diagnosis of cyanosis (Troche 1989). Intra-amniotic instillation has, however, also produced neonatal haemolytic anaemia or liver damage (Martindale 1989). Not an entirely safe substance in the last trimester, methylene blue has been implicated recently in producing fetal intestinal atresia when used in the second trimester of pregnancy.

Nicolini & Monni (1990) reported seven sets of twins in whom 1–3 ml of 1% methlene blue was used to identify the first sac sampled at amniocentesis and in whom one twin was later found to have multiple ileal obstructions. In three sets the fetal sex was discordant so the fetus receiving the methylene blue could be identified. In each case this was the one with the ileal lesions. Not all seven twin sets came from the same centre. Two were from Milan, one from London and four from Cagliari. The total number of sets of twins investigated was known only from Cagliari where in 4 of the 21 twin pregnancies (19%) the fetus given the dye to drink had ileal abnormalities at birth. An interesting and worrying observation, but the numbers were small and abnormalities do cluster. However, this observation has now been confirmed. In this issue of the Journal (p. 141) Van der Pol and his co-authors have reviewed 89 sets of twins on whom genetic amniocentesis was carried out at 16 weeks and 86 of them had 1–2 ml of 1% methylene blue injected into the first sac. Of these 178 twins 17 (9·5%) had atresia of the jejunum: in 13 there were multiple areas of atresia with mesenteric gaps. All had normal chromosomes and normal levels of alpha-fetoprotein in the amniotic fluid obtained at amniocentesis. In 15 of the pregnancies the twin with the atresia could be identified as the one who received the methylene blue. Not only do these larger numbers corroborate the original observation but their validity is increased by the accompanying review of all babies with jejunal atresia born in the Netherlands over the same period, 1986–1990. There were 67 affected babies and 20 were one of a set of twins. In 19 of these 20 affected twin babies amniocentesis had been performed and a dye used: methylene blue in 18 and indigo carmine in one.

To stop using methylene blue for the identification of amniotic sacs would not endanger antenatal diagnosis in the United Kingdom. Ultrasound can now define individual sacs with certainty so an additional marker is not required. Where less advanced ultrasound is used or no ultrasound is available a method of identifying the first sac may well be necessary. In this issue of the journal (p. 126) Beekhuis and colleagues suggest that a membrane-free haemolysate of maternal blood be used. They instilled it safely into 63 sacs at second trimester amniocentesis. However, the preparation of the haemoglobin solution does require sonification, centrifugation and filtration and such facilities may not be available in centres where a marker must be used. Dyes are easy to use but are other dyes any safer than methylene blue? Evans blue has been used to measure circulating volume in the newborn baby without harm (Jegier *et al.* 1964), and for measuring amniotic fluid volume safely (Gadd 1969). It is, however, no longer available. Indigo carmine is a vasoconstrictor like methylene blue (Erickson & Widmer 1968), and might produce similar fetal abnormalities. It may have done so in one case in the Netherlands reported by Van der Pol in this issue (p. 141). There is no large clinical study of indigo carmine but it has been instilled into more than 100 amniotic sacs at second trimester amniocentesis without reported ill-effects (Elias *et al.* 1980, Pijpers *et al* 1988). This appears to be the current dye of choice but its use should be monitored since its apparent relative safety may be only the result of the small numbers reported. It might also be used in other situations. Detection of ruptured membranes by instilling dye into the amniotic cavity is established practice (Atlay & Sutherst 1970). The occasional neonatal problem following methylene blue suggests that other dyes should be investigated. A well conducted trial of indigo carmine would be worthwhile. To discover another substance that was free of all risks would be more valuable.

Iain McFadyen

Senior Lecturer
Department of Obstetrics and Gynaecology
The University of Liverpool
Liverpool L7 8XP

References

Atlay R. D. & Sutherst J. R. (1970) Premature rupture of the fetal membranes confirmed by intra-amniotic injection of dye (Evans blue T-1824) *Am J Obstet Gynecol* **108**, 993–994.

Beekhuis J. R., de Bruijn H. W. A., van Lith J. M. M. & Mantingh A (1992) Second trimester amniocentesis in twin pregnancies: maternal haemogolobin as a dye marker to differentiate diamniotic twins, *Br J Obstet Gynaecol* **99**, 126-127.

Elias S., Gerbie A. B., Simpson J. L., Nadler H L., Sabbagha R E. & Shkolnik A. (1980) Genetic amniocentesis in twin gestations *Am J Obstet Gynecol* **138** 169-174.

Erickson J C. & Widmer B. A. (1968) The vasopressor effect of indigo carmine. *Anesthesiolgy* **29**, 188.

Gadd R. (1966) The volume of the liquor amnii in normal and abnormal pregnancies. *J Obstet Gynaecol Br Cwth* **73**, 11-22

Jegier W., McLaurin J., Blakenship W. & Lind J. (1964) Comparative study of blood volume estimation in the newborn infant using ^{131}I-labelled human serum albumin (RIHSA) and T-1824 *Scand J Clin Lab Invest* **16**, 125-132.

Martindale (1989) *The Extra Pharmacopoeia* (Reynolds J. E. F., ed.), 29th edition, The Pharmaceutical Press, London.

Nicolini V. & Monni G. (1990) Intestinal obstruction in babies exposed in utero to methylene blue (letter). *Lancet* **336**, 1258.

Pijpers L., Johoda M. G. J , Vosters R. P. L., Niermeijer M F. & Sachs E. S. (1988) Genetic amniocentesis in twin pregnancies. *Br J Obstet Gynaecol* **95**, 323-326.

Troche B I. (1989) The methylene blue baby (letter). *N Engl J Med* **320**, 1756-1757.

Van der Pol J. G , Wolf H., Boer K., Treffers P. E., Leschot N. J , Hey H. A. & Vos A. (1992) Jejunal atresia related to the use of methylene blue in genetic amniocentesis in twins. *Br J Obstet Gynaecol* **99**, 141-143.

British Journal of Obstetrics and Gynaecology
February 1992, Vol. 99, pp. 90–91

Confidence intervals for research findings

Medical research is based on the study of a sample of individuals, which is used as the basis for making statements about the wider population. Thus, for example, a study of pregnancy will take a sample of pregnant women and use the results to make statements (inferences) about all pregnant women. The choice of sample does not usually get sufficient attention in medical research, yet valid inferences depend crucially upon having a representative sample. The statistical ideal of a random sample is almost never feasible. It is therefore usually assumed that a series of consecutive patients in a single centre (such as a hospital) will be sufficiently representative. While this is likely to be reasonable for a sample of pregnant women, it may not be for a sample of patients with a particular disease, depending on whether the hospital is a specialist referral centre for that disease. There may of course be pre-defined reasons, such as concurrent illness or multiple pregnancy, for excluding some subjects from such a sample. It is thus very important that research papers describe clearly the source of the sample of subjects, and any selection criteria.

Because humans vary greatly even a representative sample may yield results that differ from the true situation in the relevant population. If several samples are taken (or replicated studies are carried out) we expect to get different results from each, although they ought to be reasonably close if the samples are all representative. It is common for the results of independent studies to disagree, although the larger the samples are the more similar the results should be.

If we make certain assumptions we can obtain from a single sample a measure of uncertainty about our inferences. A result from a sample is known as an estimate and the uncertainty associated with it can be expressed as a *confidence interval*. In recent years estimation and confidence intervals have found increasing favour over hypothesis testing in medical journals (e.g., Gardner & Altman 1986; Bulpitt 1987; Braitman 1991) Our aim here is to explain and contrast these alternative approaches to statistical inference.

Hypothesis testing (more often called significance testing) leads to *P* values, which are very familiar. However, there is much evidence to suggest that despite familiarity the meaning of the *P* value is not well understood. In a hypothesis test we negate the research hypothesis to get a *null* hypothesis. For example, if we wish to test whether one treatment is superior to another we start with the null hypothesis that the two treatments are equally effective. We then calculate the probability of getting the observed data (or more unlikely data) if the null hypothesis was in fact true—this probability is the *P* value. If *P* is very small we reject the null hypothesis in favour of the alternative (research) hypothesis, for example that the two treatments are not equally effective. If *P* is very large we should not conclude that equality has been demonstrated, but rather that there is no evidence to reject this possibility. By convention a value of *P* smaller than 0·05 (i.e. 5%) is called *significant*. This arbitrary cutpoint is widely overused to determine which results can be considered real or medically important, although such an interpretation is not necessarily warranted. The *P* value by itself tells us nothing about the size of an effect or difference, nor even the direction of the difference. For this reason it is not acceptable to the *British Journal of Obstetrics and Gynaecology* to present results of a study solely as *P* values. Likewise, *P* values on their own in abstracts are not informative as they do not indicate the magnitude (or direction) of observed effects.

By contrast, the estimation approach aims to quantify not only the effect of interest but also the uncertainty in this estimate by means of a confidence interval. Most often this is a range of values either side of the estimate in which we can be 95% sure that the true value lies, although other percentages (most often 90% or 99%) are sometimes used. A confidence interval gives a measure of the precision (or uncertainty) of study sample results for making inferences about the population. Confidence intervals may be especially useful in small samples, and also to avoid the misinterpretation of non-significant results ($P>0{\cdot}05$) by showing that the data are compatible with clinically useful true effects.

These methods are not new, nor is the advocacy of their use in medical research (Wulff 1973; Rothman 1978), but it is only recently that the advantages of this approach over hypothesis testing have become more widely appreciated. Their use is now recommended by several journals, and they have been encouraged in our instructions to authors since 1986 (see 'Directions to Contributors'). The *British Medical Journal* requires their use when appropriate (and feasible) for the main results of a study, and the *British Journal of Obstetrics and Gynaecology* will adopt the same stance in future.

We emphasise that confidence intervals are desirable for the primary results of a study; they are not needed for all results. Further, it is important that when given they relate to the contrast of interest. For example, when two groups are compared the appropriate confidence interval is that for the difference between the groups. It is not usually useful to give separate confidence intervals for the estimates in each group.

The advantages of confidence intervals can best be seen using examples from papers published recently in this Journal. Kovacs *et al.* (1991) compared serum testosterone levels in ten women before and after ovarian electrocautery for polycystic ovarian syndrome. The mean change was −0·65 nmol/l (SE 0·21), giving $P = 0{\cdot}011$. Although highly statistically significant, because of the small sample size the 95% confidence interval for the mean change is wide, going from −1·13 to −0·18 nmol/l indicating considerable uncertainty about the average effect of electrocautery. Chanoine *et al.* (1991) quote a correlation coefficient of 0·37 between cord serum thiocyanate and thyroglobulin concentrations ($P = 0{\cdot}001$) in 82 newborn infants. Although the *P* value is very small, the association is not all that strong. The 95% confidence interval for the correlation coefficient is from 0·17 to 0·54, showing that the strength of the association is not precisely estimated in this size of study.

Hjalmarson *et al.* (1991) reported a comparative study of women smokers who were given a self-help manual aimed at getting them to stop smoking and a control group who were given just an information sheet and a recommendation to stop smoking. In the treatment group 46/444 (10%) were continuously abstinent throughout pregnancy, compared to 11/209 (5%) in the control group. The odds ratio was correctly and usefully reported for comparison between groups as 0·5 with a 95% confidence interval from 0·2 to 0·9 (although it would be more usual to consider odds in the treatment group relative to those in the control group, giving an odds ratio of 2·0). An alternative approach would have been to use the relative risk, which gives very similar answers for these data. However, Hjalmarson *et al.* (1991) reported some of their results without direct between group comparisons. For example, the mean birthweights of babies in the two groups were reported as 3430 g (95% CI: 3378 to 3483 g) in the treatment group and 3359 g (95% CI: 3286 to 3433 g) in the control group. As noted above, it would have been more appropriate to give the difference in mean birthweight of 71 g with its 95% confidence interval of −21 g to 163 g, which demonstrates directly the uncertainty about the magnitude of the relative effects of the two interventions.

Methods for calculating confidence intervals for many types of data are given in Gardner & Altman (1989), and a computer program for personal computers (CIA) is available from the *British Medical Journal* (Gardner *et al.* 1989). We do not think that the time is yet right to abandon *P* values (Evans *et al.* 1988); however, nor do we think that they should always be included in statistical presentation. It is likely that most papers that use statistical methods will contain both confidence intervals and *P* values, the first being more useful.

Douglas G. Altman
Medical Statistics Laboratory
Imperial Cancer Research Fund
PO Box 123
Lincoln's Inn Fields
London WC2A 3PX
Martin J. Gardner
MRC Environmental Epidemiology Unit
(University of Southampton)
Southampton General Hospital
Southampton SO9 4XY

References

Braitman L. E. (1991) Confidence intervals assess both clinical significance and statistical significance. *Ann Intern Med* **114**, 515–517.

Bulpitt C. J. (1987) Confidence intervals. *Lancet* **i**, 494–497

Chanoine J. P., Toppet V., Bourdoux P., Spehl M. & Delange F. (1991) Smoking during pregnancy: a significant cause of neonatal thyroid enlargement. *Br J Obstet Gynaecol* **98**, 65–68.

Evans S. J. W., Mills P. & Dawson J. (1988) The end of the p value? *Br Heart J* **60**, 177–180.

Gardner M. J. & Altman D. G. (1986) Confidence intervals rather than P values: estimation rather than hypothesis testing. *Br Med J* **292**, 746–750.

Gardner M. J. & Altman D. G. (1989) *Statistics With Confidence*. British Medical Journal, London.

Gardner M. J., Gardner S. B. & Winter P. D. (1989) *Confidence Interval Analysis (CIA) Microcomputer Program Manual*. British Medical Journal, London.

Hjalmarson A. I. M., Hahn L. & Svanberg B. (1991) Stopping smoking in pregnancy: effect of a self-help manual in controlled trial. *Br J Obstet Gynaecol* **98**, 260–264.

Kovacs G., Buckler H., Bangah M., Outch K., Burger H., Healy D., Baker G & Phillips S. (1991) Treatment of anovulation due to polycystic ovarian syndrome by laparascopic ovarian electrocautery. *Br J Obstet Gynaecol* **98**, 30–35.

Rothman K. (1978) A show of confidence. *N Engl J Med* **299**, 1362–1363.

Wulff H. R. (1973) Confidence limits in evaluating controlled trials. *Lancet* **ii**, 969–970.

British Journal of Obstetrics and Gynaecology
February 1992, Vol. 99, pp. 92–93

Confined, managed and delivered: the language of obstetrics

Some public criticisms in recent years have characterized obstetric services and practices as dehumanizing and insensitive to women's needs and feelings. However, the description of care as 'insensitive' is diffuse, and it can be hard to specify why women sometimes perceive their care in this way. Identifying constructive and feasible changes that would improve the quality of the experience is, therefore, particularly difficult. Occasionally the grounds for criticisms of professional behaviour may seem inexplicable or even ridiculous to the professionals themselves. Yet practices that are second nature and, therefore, no longer visible to professionals may, nevertheless, be alienating and disturbing to 'outsiders'. The language used by a professional group is one such example.

The jargon of obstetrics, that we have inherited, was never designed with the sensibilities of pregnant women in mind. While it can be readily understood, the message received can be quite devastating. As a non-medical consumer, I am constantly amazed at the list of things women are told they have 'failed' at: they can 'fail' to dilate, to progress, to home birth, to breastfeed—and their babies can 'fail' to thrive. Bits and pieces of them can 'fail' as well: contractions can be 'inadequate', as can their pelvis. Their cervix can be 'incompetent' (or merely 'unfavourable'). In the language of obstetrics and gynaecology, it is even possible for mucus to be 'hostile'! Such language is not 'consumer friendly', and must surely contribute to women's perceptions that practitioners are insensitive.

Macintyre (1982) identifies three distinctive features of the maternity services that predispose towards criticism and resentment of poor communications with attendants. The first is the amount of routine 'processing' involved in the care of pregnant women. Second, those using the services are generally not ill. Finally, she highlights the discrepancy between what women are encouraged to expect in terms of having their questions answered, and the reality of the experience of hospital wards.

A fourth feature should be added—the sexuality of the experience of childbirth. The need to render intimate contact and discussion safe and comfortable for both the obstetrician and the pregnant or labouring woman necessarily involves a degree of formalization. Finding the appropriate balance between seeming neither over-familiar nor impersonal to an individual woman will often be difficult. Further, as one obstetrician cautions, it is possible that efforts to rid consultations of sexual connotations can lead to a narrow distorted perspective of a pregnant woman, with the relationship 'not only desexualized, but virtually dehumanized. It has become "clinical" in the very *worst* sense of the word' (Myerscough 1989).

The use of depersonalizing language and the terminology of failure and inadequacy may adversely affect a woman's confidence and self-esteem. Feeling ineffectual and impotent will not be helpful to a woman in coping with the stresses of labour and motherhood. Nor should women be left with a view of their bodies as faulty machines, or their personal responses and 'performance' as inadequate. Indeed, the language of failure and structural dysfunction may be appropriate when applied to a machine or even a process—for example, failed induction, but it is inappropriate when applied to a woman.

A reductionist approach may be essential to identify physical factors that are contributing to difficulties in labour, but it is critical that caregivers do not lose sight of the whole person and her needs. This is particularly important when communicating with others in her presence. The practice of defining pregnant women by their 'conditions' may be convenient and informative between professionals, but it is quite literally depersonalizing. In this context, an entire human being and her child can be reduced to 'a prolapsed cord'. An unintended effect of this may well be to reduce a woman's sense of personal significance.

A mechanistic approach to defining childbirth is also reflected in the tendency to describe events not in terms of women's actions, but from the point of view of the 'operators'. The woman's role becomes so passive that it is invisible in the terminology: instead of women labouring, being cared for, and giving birth, they are 'confined', 'managed', and 'delivered'. These terms and their connotations of restriction, passivity of the woman, and control and heroism of the caregiver are surely anachronisms. Childbirth is momentous both for the woman giving birth and the child being born. Regardless of the amount of assistance, this is the central reality which should define the event—not the assistance.

The language of obstetrics is also heir to the terminology of medicine generally, sometimes with unfortunate consequences. Military jargon seems to be common throughout medical practice, with diseases and symptoms being 'attacked' with a medical 'armamentarium'. While the need to 'defuse' the intimacy and sexuality of birth among professionals may be necessary to some extent, adopting military metaphors is certainly going too far It is, for example, surely 'overkill' to describe a baby's head as 'a battering ram' against a 'rigid and unyielding' perineum. It would seem reasonable to suspend the language of hostility when dealing with sexuality and with birth. Certainly a less confronting adjective than 'hostile' should be used to describe mucus which may be contributing to infertility—and preferably it should not be replaced with 'spermicidal'!

On occasion, an examination of somewhat aggressive language may reveal ways of thinking about care which are inappropriate in themselves. 'Allowing' a woman a 'trial' of labour, for example. Women in a variety of situations need intensive monitoring and have a greater probability of needing obstetric intervention. Why is it necessary to tell one particular group of women that they are 'on trial' and regard them in this way? Indeed, it is hard to imagine any circumstance in which it is appropriate to put a woman or her uterus 'on trial' (after a second stage 'arrest' perhaps!)

Technical descriptions that have an emotional loading in ordinary use may also need to be avoided: for example, the inclusion of the word 'retardation' in the expression 'intrauterine growth retardation' may possibly communicate a message other than that intended. Explanations and descriptions should also be given at a level of complexity and technicality appropriate to the woman concerned. Whereas it can be quite easy to either under-estimate or over-estimate a particular person's level of comprehension, some terms are never appropriate. Despite the fact that even at only 36 they may already be described as 'elderly', women in labour are still called 'girls' and even addressed in baby talk—'Just pop in and do a little wee, there's a good girl.'

Macintyre (1982) highlights the frequent use of euphemisms to pregnant and labouring women, with terms such as 'the waterworks' and 'down there' being common. She points out that this typically underestimates women's understanding and knowledge, and the use of euphemistic language can result in confusion—the terms are highly unproductive because of their vagueness.

There have been some important improvements in the terminology used in obstetrics and gynaecology, such as the language of infertility moving beyond reliance on the terminology of 'barrenness' and 'sterility'. Another improvement was abandoning the term 'labour pains' in favour of 'contractions', effectively moving the focus of childbirth to its labour rather than just the pain.

Substitute terminology needs to remain informative and descriptive to be useful, and can involve quite simple changes. In reporting perinatal outcomes among planned home births in Australia, for example, 'failure to progress' became 'lack of progress', 'management' was replaced by 'care', and vaginal births after previous caesarean sections were 'planned' rather than 'attempted' (Bastian & Lancaster 1990).

Finding feasible and acceptable alternative terminology is easier than changing habits ingrained in training and by long usage. However, while the evolution of language can be a slow process, the use of jargon is also a matter of personal choice. A starting point is that individual professionals should become more self-conscious of the impact on pregnant women of the language of obstetrics and the attitudes expressed by its use. Obstetricians and midwives need to begin really hearing what their language sounds like to an outsider, and to feel uncomfortable where terminology is clearly inappropriate.

The experience of childbirth is becoming less 'confining' for individual women: it is time to address the language to ensure that it reflects this evolution. At the very least, the elimination of the language of failure, inadequacy and incompetence is well overdue.

Hilda Bastian
P O Box 314
Katoomba, NSW 2780
Australia

References

Bastian H & Lancaster P. A. L. (1990) *Home Births in Australia 1985–1987* National Perinatal Statistics Unit, Sydney.

Macintyre S. (1982) Communications between pregnant women and their medical and midwifery attendants. *Midwives Chronicle and Nursing Notes* pp. 387–394.

Myerscough P. R. (1989) *Talking with Patients: A Basic Clinical Skill*, Oxford University Press, Oxford.

British Journal of Obstetrics and Gynaecology
February 1992, Vol. 99, pp. 93–95

Why might maternal serum AFP be high in pregnancies in which the fetus is normally formed?

Maternal serum alpha-fetoprotein (AFP) screening programmes for neural tube defects (NTDs) have been operating for approximately 15 years in a number of centres (Ferguson-Smith 1983; Wald *et al* 1979). It is clear that as well as indicating an increased risk for an ever-growing list of fetal anomalies, an elevated maternal serum AFP measured during the second trimester, in the absence of malformation or uncertain gestation, also indicates an increased-risk of multiple pregnancy, miscarriage, stillbirth, neonatal death and low birthweight (Gilmore & Aitken 1989).

Little is known about the biological function of AFP although its molecular structure, development and kinetics are well studied (Gitlin 1975; McKusick 1990). It has never been shown that a raised AFP in itself is damaging and its use in obstetrics has been merely that of a marker. AFP is a major fetal protein, relative molecular mass 65 kD, allowing limited transplacental transfer (Morriss & Boyd 1989). AFP and albumin have similar physical properties and they occur in inverse concentrations, suggesting that AFP is the fetal form of serum albumin. Initially AFP, along with other proteins, is formed by the yolk sac and then by the fetal liver with a much smaller contribution from the gastrointestinal tract. Peak concentration of AFP in the fetus occurs at the end of the first trimester. The concentration of fetal plasma AFP decreases from 14 weeks because production of AFP, although actually increased in amount, declines per unit weight of fetus. After approximately

32 weeks gestation, AFP synthesis declines rapidly with a precipitate fall in fetal plasma AFP. In the absence of rare pathology (e.g., hereditary persistence of AFP, an autosomal dominant trait, Ferguson-Smith 1983), AFP synthesis virtually ceases at birth but minute amounts are detectable throughout life.

Maternal serum AFP concentration is approximately 50 000 times lower and lags behind that in the fetus, rising from weeks 10 to 32 and declining thereafter. Although maternal serum AFP is rising while fetal AFP is on the decline, a huge concentration gradient always exists from fetus to mother. Amniotic fluid AFP concentration runs parallel to fetal concentration but is approximately 150 times lower.

Theoretically the fetal to maternal transfer of AFP occurs by two routes, first transplacental, the rate depending not only on the permeability of the placenta but also directly on the concentration gradient, the villous surface area and inversely on the thickness of the barrier (i.e., the distance separating the fetal and maternal circulations). The level of maternal serum AFP also depends on the size of (and hence the AFP dilution within) the maternal vascular compartment and the clearance of AFP from it. Fetuses associated with a high maternal serum AFP do not (with very rare exceptions) have a high concentration themselves. The raised levels of maternal serum AFP found in twin pregnancies can probably be explained by this first route because of a large villous surface area.

The second route is transmembraneous. AFP probably enters the amniotic fluid initially by diffusion through poorly keratinized fetal skin (Seller & Berry 1978) and, following the development of glomerular filtration, in fetal urine. There has been some debate about the importance of this route compared to the first but in the absence of fetal abnormality such as NTD (with raised amniotic fluid levels of AFP) it seems that the transmembrane route makes a minor contribution to maternal serum AFP (Los *et al.* 1985).

Study of the placenta both macroscopically, microscopically and by ultrasound scan has given some insight into the reasons why maternal serum AFP may be raised in association with a normally formed fetus. Any factor allowing feto-maternal haemorrhage (i.e., a breakdown in the fetal maternal barrier, spontaneous or induced by CVS or amniocentesis) will cause an elevation of maternal serum AFP and indeed the level of maternal serum AFP provides a sensitive indication of this (Hay *et al.* 1979; Fuhrmann *et al.* 1988). Villous surface area increases throughout gestation in normal pregnancies (Boyd 1984), although the rate of growth decreases from 34 weeks. This provides some explanation for the reason why maternal serum AFP increases up to 32 weeks gestation inspite of reduced fetal AFP synthesis (and assuming negligable maternal synthesis). Between 20 and 32 weeks villous surface area increases approximately 5·5 times, maternal serum AFP increases nine times and fetal plasma AFP concentration falls seven times. It seems that there must be an increase in placental permeability during the second trimester to account for the rise in maternal serum AFP in normal pregnancy. In a small morphometric study of placentas associated with raised maternal serum AFP, a normal concentration of amniotic fluid AFP, and a normally formed fetus, the mean total placental volume, volume of parenchyma and villous surface area were increased, there were more areas of infarction and a lower fetal-placental weight ratio compared with a control group in which the maternal serum AFP was not elevated (Boyd & Keeling 1986). Increased transport of AFP across the large villous surface area seems a likely explanation and perhaps some increase in placental permeability in those placentas which at delivery show areas of infarction. The increase in villous surface area may be a response to an adverse intrauterine environment. Pre-eclampsia, placental abruption and infarction, chronic villitis, low birthweight and maternal cigarette smoking have all been associated with raised maternal serum AFP (Walters *et al.* 1985; Salafia *et al.* 1988; Brock *et al.* 1977; Cuckle *et al.* 1990). All of these conditions may be associated with abnormalities in the placenta or in placentation. For example abnormal placentation is known to precede the onset of symptoms or signs of pre-eclampsia (Robertson 1981). Such pregnancies are therefore compromised during or before the second trimester. It must be remembered that for most studies relating placental factors to raised maternal serum AFP some 24 weeks may have passed from measurement of AFP to examination of the placenta. However, using ultrasound examination, Perkes *et al.* (1982) found that more placentas in pregnancies with a high maternal serum AFP had sonolucent spaces on ultrasound scan during the second trimester than those with a normal serum AFP, although the numbers studied were small. They postulate that these spaces act as conduits allowing fetal blood to enter the maternal circulation.

A suboptimal fetoplacental unit is reflected in the relatively poor outcome of these pregnancies. There have been many studies over the last 15 years (recently confirmed in a large study by Milunsky *et al.* 1989) showing that normally formed fetuses associated with a raised serum AFP are at a greater risk of neonatal death and newborn complications, stillbirth, low birthweight, oligohydramnios, placental abruption, pre-eclampsia and miscarriage. In spite of these increased risks approximately half of those fetuses associated with a serum AFP above two multiples of the median (MOMs) will be liveborn and have an uneventful neonatal period (Brock *et al.* 1979) so that it has been suggested by some (Rodeck *et al.* 1976) that AFP is not a reliable test for predicting fetal wellbeing. However, the proportion of those with an entirely 'normal' outcome falls dramatically as the maternal serum AFP rises, being only 9% if 4 MOMs are used as a cut-off, suggesting that the lower the raised serum AFP value the more likely it is to represent the top of the normal range. Using a higher cut-off provides a good prediction of pregnancies at risk.

The reasons maternal serum AFP at 16 weeks gestation may be raised in association with a normally formed fetus can be attributed mainly to changes in the placenta which has the property of responding to an adverse environment by increasing its surface of exchange. An increase in permeability probably explains some cases. AFP has proved extremely useful in the detection of fetal anomaly. Its place as a placental function test should not be ignored and it could usefully focus attention on our lack of knowledge of some areas of placental physiology.

P. A. Boyd
Senior Registrar to Professor Edwards
Department of Medical Genetics
Churchill Hospital
Headington
Oxford OX3 7LJ

References

Boyd P. A. (1984) Quantitative structure of the normal human placenta from 10 weeks of gestation to term. *Early Hum Dev* **9**, 297-307.

Boyd P. A. & Keeling J. W. (1986) Raised maternal serum alpha-fetoprotein in the absence of fetal abnormality—placental findings. A quantitative morphometric study. *Prenat Diagn* **6**, 369-373.

Brock D. J. H., Barron L., Jelen P., Watt M. & Scrimgeour J. B. (1977) Maternal serum alpha-fetoprotein measurements as an early indicator of low birthweight. *Lancet* **ii**, 267-268.

Brock D. J. H., Barron L., Duncan P., Scrimgeour J. B. & Watt M. (1979) Significance of elevated mid-trimester maternal plasma-alpha fetoprotein values. *Lancet* **i**, 1281-1282.

Cuckle H. S., Wald N. J., Densem J. & Royston P. (1990) The effect of smoking in pregnancy on maternal serum alpha-fetoprotein, unconjugated oestriol, human chorionic gonadotrophin, progesterone and dehydroepiandrosterone sulphate levels. *Br J Obstet Gynaecol* **97**, 272-276.

Ferguson-Smith M. A. (1983) The reduction of anencephalic and spina bifida births by maternal serum alpha-fetoprotein screening. *Br Med Bull* **39**, 365-372.

Fuhrmann W., Altland K., Kohler A., *et al.* (1988) Feto-maternal transfusionn after chorionic villus sampling. *Hum Genet* **78**, 83-85.

Gilmore D. H. & Aitken D. A. (1989) Prenatal screening. In *Prenatal Diagnosis in Obstetric Practice.* (Whittle M. J. & Connor J. M., eds) Blackwell Scientific Publications Oxford. pp. 22-23.

Gitlin D. (1975) Normal biology of alpha-fetoprotein. *Ann NY Acad Sci* **259**, 7-16.

Hay D. L., Barrie J. U., Davison G. B., Buttery B. W., Horacek I., Pepperell R. J. & Fliegner J. R. H. (1979) The relation between maternal serum alpha-fetoprotein levels and fetomaternal haemorrhage. *Br J Obstet Gyneccol* **86**, 516-520.

Los F. J., De Bruijn H. W. A., Van Beek Calkoen-Carpay T. & Huisjes H. J. (1985) AFP transport across the fetal membranes in the human. *Prenat Diagn* **5**, 277-281.

McKusick V. A. (1990) Alpha-fetoprotein. In *Mendelian Inheritance of Man* 9th ed. Catalogue number 104150, Johns Hopkin's University Press, Baltimore and London, pp. 45-47.

Milunsky A., Jick S. S., Bruell C. L., *et al.* (1989) Predictive values, relative risks, and overall benefits of high and low maternal serum alpha-fetoprotein screening in singleton pregnancies. New epidemiologic data. *Am J Obstet Gynecol* **161**, 291-297.

Morriss F. H. & Boyd R. D. H. (1988) Placental transport. In *The Physiology of Reproduction.* (Knobil E. & Neil J. D., eds) Raven Press, New York, Vol. I, pp. 2043-2083.

Perkes E. A., Baim R. S., Goodman K. J. & Macri J. N. (1982) Second-trimester placental changes associated with elevated maternal serum alpha-fetoprotein. *Am J Obstet Gynecol* **144**, 935-938

Robertson W. B. (1981) Gestational endometrium. In *The Endometrium.* Postgraduate Pathology Series. (Crawford T., ed.) Butterworth, London, pp. 73-107.

Rodeck C. H., Campbell S. & Biswass S. (1976) Maternal plasma alpha-fetoprotein in normal and complicated pregnancies. *Br J Obstet Gynaecol* **83**, 24-32.

Salafia C. M., Siberman L., Herrera N. E. & Mahoney M. J. (1988) Placental pathology at term associated with elevated midtrimster maternal serum alpha-fetoprotein concentration. *Am J Obstet Gynecol* **158**, 1064-1066.

Seller M. J. & Berry A. C. (1978) Amniotic-fluid alpha-fetoprotein and fetal renal agenesis. *Lancet* **i**, 660.

Wald N. J., Cuckle H. S., Boreham J. *et al.* (1979) Antenatal screening in Oxford for fetal neural tube defects. *Br J Obstet Gynaecol* **86**, 91-100.

Walters B. N. J., Lao, T., Smith V. & De Swiet M. (1985) Alpha-fetoprotein elevation and proteinuric pre-eclampsia. *Br J Obstet Gynaecol* **92**, 341-344.

British Journal of Obstetrics and Gynaecology
February 1992, Vol. 99, pp. 96–100

OBSTETRICS

Breech delivery and epidural analgesia

YOGESH C. CHADHA
TAHIR A. MAHMOOD
MICHAEL J. DICK
NORMAN C. SMITH
DORIS M. CAMPBELL
ALLAN TEMPLETON

Department of Obstetrics and Gynaecology
Aberdeen Maternity Hospital
Cornhill Road
Aberdeen AB9 2ZB, UK

ABSTRACT

Objective To examine the effect of epidural analgesia on the progress and outcome of spontaneous labour in women with a singleton breech presentation at term (≥37 weeks).

Design A retrospective study.

Setting Data Bank, Aberdeen Maternity Hospital.

Subjects 643 women (273 primiparae and 370 multiparae) with a singleton breech presentation and spontaneous onset of labour at term.

Outcome measures Duration of labour; augmentation of labour with oxytocin infusion; caesarean section rates.

Results Epidural analgesia was associated with a significantly increased need for augmentation of labour with oxytocin infusion ($P<0{\cdot}001$) and longer duration of labour ($P<0{\cdot}001$), irrespective of parity. Comparing women who had epidural analgesia with those who did not, there was no significant difference in caesarean section rates in the first stage of labour in primiparae (odds ratio 1·79; 95% CI 0·88–3·63) or multiparae (odds ratio 0·97; 95% CI 0·48–1·96). Epidural analgesia was associated with a significantly increased likelihood of caesarean section in the second stage of labour, both in primiparae (odds ratio 5·43; 95% CI 2·46–11·95) and multiparae (odds ratio 5·37; 95% CI 2·07–13·87). The increased likelihood of caesarean section in the second stage in primiparae with epidurals was independent of the extent of cervical dilatation (<3 cm or ≥3 cm) on admission. However, in multiparae with epidurals, the difference in second stage caesarean section rate was significant only when initial cervical dilatation was <3 cm (odds ratio 3·65; 95% CI 1·14–11·65).

Conclusion Epidural analgesia was associated with longer duration of labour, increased need for augmentation of labour with oxytocin infusion and a significantly higher caesarean section rate in the second stage of labour.

The management of full term breech presentation remains controversial. Obstetric practice varies from delivery by caesarean section always (Hall & Kohl 1956; Kubli *et al.* 1976) to vaginal delivery in selected patients (Neligan *et al.* 1974; Collea *et al.* 1980; Mahmood 1987). Epidural block provides excellent analgesia, reduces maternal and fetal acidosis (Pearson & Davies 1973 & 1974), prevents expulsive efforts before full cervical dilatation and allows the patient to be relaxed and cooperative at the time of assisted breech delivery (Confino *et al.* 1985). With a cephalic presentation epidural analgesia is associated with a prolonged second stage and an increased rate of forceps delivery (Studd *et al.* 1980). In their study of epidural analgesia in women of mixed parity with breech presentation, Bingham *et al.* (1987) observed a significantly prolonged second stage and half the failed trials of labour occurred in the second stage. It is difficult to draw firm conclusions from other studies which have examined the use of epidural analgesia in breech delivery (Bowen-Simpkins & Ferguson 1974; Breeson *et al.* 1978; Confino *et al.* 1985) because the study groups are small and heterogenous.

Correspondence: Dr Yogesh C. Chadha, Health Services Research Unit, University of Aberdeen, Drew Kay Wing, Polwarth Building, Foresterhill, Aberdeen AB9 2ZD.

This retrospective study was undertaken to examine the effect of epidural analgesia on the progress and outcome of spontaneous labour in women with a singleton breech presentation at a gestational age ≥37 weeks.

Subjects and methods

The records of 1456 women with a mature singleton breech presentation (gestational age ≥37 weeks) delivered at Aberdeen Maternity Hospital between 1979 and 1986 were identified: 540 (37%) were primiparae and 916 (63%) were multiparae. In 562 (39%) of the 1456 women delivery was by elective caesarean section (196/540 (36%) primiparae and 366/916 (40%) multiparae) and 225 (15%) had labour induced (61/540 (11%) primiparae and 164/916 (18%) multiparae).

The elective caesarean sections, inductions of labour and 26 other pregnancies (six with fetal malformation, three stillbirths, five with uterine malformation, two with placental abruption and ten with missing case notes) were excluded from further analysis. The remaining 273 primiparous and 370 multiparous women who had been selected for trial of vaginal breech delivery and had spontaneous onset of labour constituted the study group.

Table 1. Characteristics of the subjects in the study

	Primiparae		Multiparae	
	Epidural (n=175)	No epidural (n=98)	Epidural (n=142)	No epidural (n=228)
Age (years)	23·5 (0·31)	24·6 (0·40)	27·70 (0·29)	27·96 (0·26)
Height (cm)	162 (0·42)	162 (0·45)	160·60 (0·36)	161·20 (0·34)
Gestational age (weeks)	39 5 (0·09)	39·2 (0·11)	39·8 (0·08)	39·7 (0·07)
Type of breech n (%)				
Extended	117 (66)	53 (54)	83 (58)	134 (59)
Incomplete	41 (24)	30 (31)	34 (24)	46 (20)
Footling	17 (10)	15 (15)	25 (18)	48 (21)
X-ray pelvimetry n (%)	113 (65)	52 (53)	71 (50)	84 (36)
AP diameter of inlet (cm)	12·34 (0·07)	12 58 (1·02)	12·21 (0·08)	12·35 (0·10)
AP diameter of outlet (cm)	11·99 (0·08)	12·10 (0·15)	12·03 (0·11)	12·06 (0·13)

There were no significant differences between the epidural and no epidural groups among primiparae or multiparae.
Results are mean (SE) or n (%) values as appropriate.

Antenatal x-ray pelvimetry was not undertaken routinely during the study period but when it was carried out, it consisted of an erect lateral view of the pelvis from which the anteroposterior (AP) diameters of the pelvic inlet and outlet and the shape of the sacrum were determined. Ultrasonic estimation of fetal weight was not attempted.

When the women were admitted in labour, continuous electronic monitoring of the fetal heart and uterine activity was undertaken. Inadequate uterine activity was managed with an escalating intravenous infusion of oxytocin. The duration of the first stage of labour was recorded as the time from admission in labour until full dilatation of the cervix. The duration of the second stage of labour was recorded as the time interval from the identification of full dilatation of the cervix until delivery. Fetal blood pH estimations were not done during the study period.

Epidural analgesia, parenteral analgesia (pethidine or diamorphine) and inhalational analgesia (Entonox) were available for pain relief in labour. All epidurals were sited between L_2 and L_4 vertebral levels by the resident anaesthetists. In the second stage of labour women without epidural analgesia had bilateral pudendal block and perineal infiltration using 1% lignocaine. Women with epidural analgesia had 'top-ups' at the discretion of the resident anaesthetist.

There was a standing policy of non-interference until delivery of the fetal trunk. Lovset's manoeuvre was used for delivery of extended arms and the head was delivered with forceps or by the Mauriceau-Smellie-Veit manoeuvre. There were no breech extractions.

Statistical analysis was carried out using Minitab Software statistical package (Statistical Department, Pennsylvania University).

Results

Of the 273 primiparae, 175 (64%) received epidural analgesia and 98 (36%) did not. Of the 370 multiparous women, 142 (38%) had epidurals and 228 (62%) did not.

The characteristics of the different groups of subjects are compared in Table 1. There were no significant differences in maternal age or height, gestational age or type of breech presentation. A greater proportion of women who received epidural analgesia had x-ray pelvimetry but the measurements were not significantly different in the epidural and no epidural groups of primiparae or multiparae.

The outcome of trial of labour is shown in Table 2. In both parity groups cervical dilatation at first examination was less in those who had epidurals than in those who did not and a greater proportion of women who had epidurals had cervical dilatation <3 cm at first assessment. In both parity groups women who had epidurals had a longer first stage of labour and a greater proportion of them had oxytocin augmentation of labour; the duration of the second stage of labour was significantly longer in women with epidurals whether they were delivered vaginally or by caesarean section. The mean birthweight of infants was similar for women who had a vaginal delivery or an emergency caesarean section in the first or second stage of labour, irrespective of the mother's parity and whether she had an epidural or not. A significantly greater proportion of women who did not have epidurals were delivered vaginally, compared with those who had epidurals: 78/98 (80%) *vs* 83/175 (47%) for primiparae (P<0·001) and199/228 (87%) *vs* 110/142 (77%) for multiparae (P<0·05), respectively.

The relation between epidural analgesia and delivery by caesarean section in the two parity groups is shown in Table 3. Among primiparae there was no significant difference in the caesarean section rate during the first stage of labour whether or not they had an epidural. However, in the second stage 57/175 (33%) women with epidurals had a caesarean section compared with 8/98 (8%) women who did not have an epidural (P<0·001). Multiparous women had similar caesarean section rates in the first stage of labour whether or not they had an epidural but in the second stage 18/142 (13%) women with epidurals were delivered by caesarean section compared with 6/228 (3%) women without an epidural (P<0·001). Table 3 also shows the indications for the caesarean sections in labour: the main reason for resorting to caesarean section in the second stage of labour was failure to progress.

Caesarean section rates related to parity and cervical dilatation at first assessment are shown in Table 4. Women of both parity groups admitted with a cervical dilatation <3 cm had a higher rate of delivery by caesarean section in the second stage

Table 2. Outcome of trial of labour

	Primiparae		Multiparae	
	Epidural (*n*=175)	No epidural (*n*=98)	Epidural (*n*=142)	No epidural (*n*=228)
Cervical dilatation on admission				
All women (cm) (a)	3·4 (0·12)**	5·2 (0·25)	3·35 (0·09)**	4·47 (0·13)
Dilatation <3 cm (b)	103 (59%)**	30 (31%)	80 (56%)**	73 (32%)
Oxytocin augmentation (b)	64 (37%)**	12 (12%)	56 (39%)**	26 (11%)
Duration of labour (a)				
First stage (h)	8·52 (0·30)**	5·20 (0·32)	7·33 (0·48)**	4·43 (0·20)
Second stage (min)				
Vaginal deliveries	71 (5) (*n*=83)**	40 (3) (*n*=78)	32 (4) (*n*=110)**	14 (1·5) (*n*=199)
Caesarean sections	107 (6·5) (*n*=57)**	53 (10) (*n*=8)	70 (5) (*n*=18)**	45 (3) (*n*=6)
Birthweights (kg) (a)				
Vaginal delivery	3·15 (0·30)	3·10 (0·05)	3·30 (0·04)	3·24 (0·04)
Caesarean section (first stage)	3·30 (0·07)	3·32 (0·15)	3·45 (0·12)	3·47 (0·30)
Caesarean section (second stage)	3·40 (0·04)	3·15 (0·16)	3·45 (0·12)	3·47 (0·30)
Vaginal delivery (b)	83 (47%)**	78 (80%)	110 (77%)*	199 (87%)

Results are mean (SE) or *n* (%) values as appropriate.
Significance of difference between the epidural and no epidural groups: $*P<0{\cdot}05$; $**P<0{\cdot}001$, unpaired *t*-test denoted by (a) and χ^2-test denoted by (b).

if they had an epidural than if they did not but the difference was only statistically significant in multiparae (primiparae 28% *vs* 10%, odds ratio 3·52, 95% CI 0·99–12·50; multiparae 18% *vs* 5%, odds ratio 3·65, 95% CI 1·14–11·65). Women of both parity groups admitted with an initial cervical dilatation ≥3 cm had a higher rate of delivery by caesarean section during the second stage if they had an epidural than if they did not but the difference was only statistically significant in primiparae (primiparae 39% *vs* 7%, odds ratio 8·02, 95% CI 2·87–22·37; multiparae 7% *vs* 2%, odds ratio 5·27, 95% CI 0·93–29·54). The combined first and second stage caesarean section rates among primiparous women with an epidural block were similar whether the cervical dilatation was <3 cm or ≥3 cm on admission in labour (52% *vs* 53%, respectively).

Data relating to the perinatal outcome in parity groups with and without epidural analgesia are shown in Table 5. There were no significant differences in Apgar scores at 1 min and 5 min, or in the requirement for, and duration of, admission to the neonatal unit, or in the incidence of other complications of delivery.

Discussion

In the absence of randomized prospective trials, we should extract as much as we can from retrospective study of the possible effects of epidural analgesia on breech delivery. This was the objective of our study. Epidural analgesia results in a significant decrease in the uterine contraction intensity during the active phase and in the second stage of labour (Johnson *et al.* 1972) and may be inappropriate for vaginal breech delivery if the reduction in maternal expulsive effort leads to an increased incidence of breech extraction or caesarean section. Epidurals may reduce the intensity of uterine action by interfering with the neurohumoral reflex which normally results in an oxytocin surge, stimulated by dilatation of the lower birth canal (Goodfellow *et al.* 1983). In cephalic presentations, disordered uter-

Table 3. Indications for caesarean section

	Primiparae		Multiparae	
Indication	Epidural (*n*=175)	No epidural (*n*=98)	Epidural (*n*=142)	No epidural (*n*=228)
First stage				
Failure to progress	20 (11%)	7 (7%)	10 (7%)	15 (7%)
Fetal distress	13 (7%)	3 (3%)	4 (3%)	6 (3%)
Cord prolapse	2 (1%)	2 (2%)	0	2 (0·9%)
Total	35 (20%)	12 (12%)	14 (10%)	23 (10%)
Odds ratio (95% CI)	1·79 (0·88–3·63)		0·97 (0·48–1·96)	
Second stage				
Failure to progress	50 (29%)	7 (7%)	14 (10%)	5 (2%)
Fetal distress	6 (3%)	1 (1%)	4 (3%)	1 (0·4%)
Cord prolapse	1 (1%)	0		
Total	57 (33%)	8 (8%)	18 (13%)	6 (3%)
Odds ratio (95% CI)	5·43 (2·46–11·95)		5·37 (2·07–13·87)	

Table 4. Caesarean section rates related to parity and cervical dilatation at first assessment

Cervical dilatation at first assessment	Primiparae		Multiparae	
	Epidural	No epidural	Epidural	No epidural
CS in first stage				
<3	25/103 (24%)	6/30 (20%)	9/80 (11%)	13/73 (18%)
Odds ratio (95% CI)	1·28 (0·47–3·48)		0·58 (0·23–1·46)	
≥3	10/72 (14%)	6/68 (9%)	5/62 (8%)	10/155 (6%)
Odds ratio (95% CI)	1·66 (0·57–4·86)		1·27 (0·42–3·87)	
CS in second stage				
<3	29/103 (28%)	3/30 (10%)	14/80 (18%)	4/73 (5%)
Odds ratio (95% CI)	3·52 (0·99–12·50)		3·65 (1·14–11·65)	
≥3	28/72 (39%)	5/68 (7%)	4/62 (7%)	2/155 (1%)
Odds ratio (95% CI)	8·02 (2·87–22·37)		5·27 (0·93–29·54)	

ine activity can be actively managed with oxytocin augmentation, but the use of oxytocin in women with breech presentations remains contentious. In this study, despite the liberal use of oxytocin augmentation and willingness of the obstetricians to wait for the breech to descend before encouraging expulsive efforts, evident from the duration of the second stage, the incidence of caesarean section was higher among women who had an epidural block compared with those who did not. This observation contrasts with some previous reports (Bowen-Simpkins & Ferguson 1974; Crawford & Weaver 1982; Rudick *et al.* 1983) which found no increase in caesarean deliveries in women of mixed parity. Indeed, one report (Darby *et al.* 1976) commented on a 50% reduction in emergency caesarean sections among women, also of mixed parity, who had epidural analgesia. Our study highlights the important difference in outcome in primiparae and multiparae. In cephalic presentations delayed maternal pushing has been advocated for women with an epidural but Buxton *et al.* (1988) found that delayed pushing in the second stage of labour failed to reduce the need for rotational forceps delivery. Furthermore, oxytocin augmentation during the second stage did not correct malposition of the fetal head (Saunders *et al.* 1989). We accept that the duration of the second stage of labour has been prolonged up to 4 h with no adverse effect on the mother or fetus in cephalic presentations (Smith *et al.* 1982), but such a policy cannot be endorsed in the management of women with a breech presentation because a prolonged second stage may then be an indication of disproportion, calling for delivery by caesarean section.

In this retrospective study there was an important difference between the groups of women with and without epidurals, relevant to interpretation of the results. Women who received epidural analgesia were less advanced in labour, in terms of cervical dilatation, at the time of admission. Therefore, it could be argued that an element of dysfunctional labour was responsible for an increased need for epidural analgesia, as well as for a higher caesarean section rate. This contention could be supported by the knowledge that in cephalic presentations an unfavourable cervical score is associated with a high caesarean section rate (Calder 1981). However, among the primiparae in

Table 5. Neonatal outcome

Outcome	Primiparae Epidural (*n*=175)	Primiparae No epidural (*n*=98)	Multiparae Epidural (*n*=142)	Multiparae No epidural (*n*=228)
Apgar score at 1 min				
≤3	11 (6%)	5 (5%)	10 (7%)	15 (7%)
4–6	41 (23%)	34 (35%)	32 (23%)	55 (24%)
≥7	123 (70%)	59 (60%)	100 (70%)	158 (69%)
Apgar score at 5 min				
≤3	0 (0)	0 (0)	0 (0)	0 (0)
4–6	6 (3%)	4 (4%)	2 (1%)	3 (1%)
≥7	169 (97%)	94 (96%)	140 (99%)	225 (99%)
Stay in neonatal unit (h)				
<24	8 (5%)	9 (9%)	4 (3%)	14 (6%)
25–48	5 (3%)	2 (2%)	8 (6%)	11 (5%)
>48	5 (3%)	3 (3%)	4 (3%)	8 (4%)
Complications				
Mild hypoxia	10 (6%)	6 (6%)	13 (9%)	4 (2%)
Jaundice	2 (1%)	1 (1%)	2 (1%)	6 (3%)
Soft tissue trauma	1 (0·6%)	2 (2%)	1 (1%)	0
All three complications	6 (3%)	5 (5%)	2 (1%)	1 (0·5%)

None of the differences between epidural and no epidural groups was statistically significant among primiparae or multiparae.

the epidural group the proportion delivered by caesarean section was similar whether the cervical dilatation was <3 cm or ⩾3 cm at first examination.

In this study, epidural analgesia was associated with longer duration of the first and second stages of labour, an increased requirement for oxytocin augmentation and a significantly higher rate of caesarean section in the second stage of labour.

Acknowledgments

We are grateful to Drs M. E. Tunstall and F. Knox, consultant anaesthetists, Aberdeen Maternity Hospital for helpful criticism and to Mrs Olive Emslie for typing the manuscript.

References

Bingham P., Hird V. & Lilford R. J. (1987) Management of the mature selected breech presentation. an analysis based on the intended method of delivery. *Br J Obstet Gynaecol* **94**, 746-752.

Bowen-Simpkins P. & Ferguson I. L. C. (1974) Lumbar epidural block and the breech presentation. *Br J Anaesth* **46**, 420-424.

Breeson A. J., Kovacs G. T., Pickles B. G. & Hill J. G. (1978) Extradural analgesia—The preferred method of analgesia for vaginal breech delivery. *Br J Anaesth* **50**, 1227-1229.

Buxton E. J., Redman C. W. E., Obhrai M (1988) Delayed pushing with lumbar epidural in labour—does it increase the incidence of spontaneous delivery? *J Obstet Gynaecol* **8**, 258-261.

Calder A. A. (1981) The human cervix in pregnancy and labour. In *The Cervix in Pregnancy and Labour.* (Elwood D. A. & Anderson A. B. M., eds), Churchill Livingstone, Edinburgh, p. 103.

Collea J. V., Chein C. & Quilligan E. J. (1980) The randomised management of term frank breech presentation. A study of 208 cases. *Am J Obstet Gynecol* **137**, 235-244.

Confino E., Ismajovich B., Rudick V. & David M P (1985) Extradural analgesia in the management of singleton breech delivery. *Br J Anaesth* **57**, 892-895.

Crawford J. S. & Weaver J. B. (1982) Anaesthetic management of twin and breech deliveries. *Clin Obstet Gynaecol* **9**, 291-296.

Darby S., Thornton C. A. & Hunter D. J. (1976) Extradural analgesia in labour when the breech presents. *Br J Obstet Gynaecol* **83**, 35-38.

Goodfellow C F., Hull M. R. G., Swab D. F., Dogterom J. & Buijs R. M. (1983) Oxytocin deficiency at delivery with epidural analgesia. *Br J Obstet Gynaecol* **90**, 214-219.

Hall J. E. & Kohl S (1956) Breech presentation. *Am J Obstet Gynecol* **72**, 977-988.

Johnson L. W, Winter W. W., Eng M., Bonica J. J., Hunter C A. (1972) Effect of pudendal, spinal, and peridural block anaesthesia on the second stage of labour. *Am J Obstet Gynecol* **113**, 166-173.

Kubli F., Boss W. & Ruttgers H. (1976) Caesarean section in the management of singleton breech presentation. In *Perinatal Medicine* (Rooth G. & Bratteby L. E., eds), Almqvist & Wiskell, Stockholm, pp. 69-75.

Mahmood T. A. (1987) Radiological pelvimetry and the management of breech presentation at term. A retrospective study *J Obstet Gynaecol* **8**, 119-123.

Neligan G. A., Prudham D. & Steiner H. (1974) *The Formative Years, Births, Family and Development in Newcastle Upon Tyne.* Oxford University Press, London, pp. 24-34.

Pearson J. F & Davies P. (1973) The effect of continuous lumbar epidural analgesia on maternal acid-base balance and arterial lactate concentration during the second stage of labour. *J Obstet Gynaecol Br Cwlth* **80**, 225-229

Pearson J F. & Davies P. (1974) The effect of continuous lumbar epidural analgesia upon fetal acid-base status during the second stage of labour *J Obstet Gynaecol Br Cwlth* **81**, 975-979.

Rudick V., Niv D., Golan A., Hethman M., Galon A., David M. P & Chayen M. S (1983) Epidural analgesia during labour in 1200 monitored parturients. *Isr J Med Sci* **19**, 20-24.

Saunders N. J., Spiby H., Gilbert L., *et al* (1989) Oxytocin infusion during second stage of labour in primiparous women using epidural analgesia. a randomised double blind placebo controlled trial *Br Med J* **299**, 1423-1426

Smith A. R. B., James D. K., Faragher E. B., Gilfillan S. (1982) Continuous lumbar epidural analgesia in labour—does delaying pushing in second stage reduce the incidence of instrumental delivery? *J Obstet Gynaecol* **2**, 170-172.

Studd J. W. W., Crawford J. S , Duigan N. M., Rowbotham C J F. & Hughes A. D (1980) The effect of lumbar epidural analgesia on the rate of cervical dilatation and the outcome of labour of spontaneous onset. *Br J Obstet Gynaecol* **87**, 1015-1021.

Received 22 October 1990
Accepted 20 October 1991

British Journal of Obstetrics and Gynaecology
February 1992, Vol. 99, pp. 101–104

OBSTETRICS

Pregnancy in sickle cell disease in Bahrain

AFFAF M. EL-SHAFEI
Chairperson, Department of Obstetrics & Gynaecology and Assistant Professor
JAGJEEVAN KAUR DHALIWAL
Consultant Obstetrician and Gynaecologist
AMARJEET KAUR SANDHU
Consultant Obstetrician and Gynaecologist

Salmaniya Medical Centre
Arabian Gulf University
State of Bahrain, Arabian Gulf

ABSTRACT

Objective To review the maternal and fetal complications in pregnant women with sickle cell disease and to compare their pregnancy outcome with those of controls.
Design A case-control study.
Setting Ministry of Health hospitals in Bahrain.
Subjects 147 pregnancies in 140 women with sickle cell disease and 294 controls matched for age and parity
Main outcome measures The characteristics of women who had crises, the frequency of the crises, hypertensive disorders of pregnancy, infection, diabetes, perinatal mortality and the delivery statistics in the index and control women.
Results Maternal mortality was 1·4% and perinatal mortality was 73·3/1000 total births in women with sickle cell disease, there were no maternal deaths and the perinatal mortality was 6·8/1000 births in the control group. Anaemia was treated by blood transfusion in 47% of women with sickle cell disease and, of these, 39% had a crisis that appeared to have been precipitated by the transfusion in the absence of any other predisposing factors. The presence of raised HbF did not decrease the number of crises but reduced their severity.
Conclusion Pregnancy in women with sickle cell disease should be monitored very closely as it constitutes a high risk to both the mother and the baby.

The overall prevalence of sickle cell disease (haemoglobin SS, SB Thal, SD and SO) in Bahrain is about 2·1% in the general population (El-Shafei *et al.* 1988a). A pregnant woman with sickle cell disease is potentially at serious risk of a sickling crisis, infections, anaemia, severe pregnancy induced hypertension and even death (Tuck & Studd 1983). We review the maternal and fetal complications and pregnancy outcome in women with sickle cell diseases.

Subjects and methods

Information was analysed from all women with sickle cell disease and from matched control women who booked and/or were delivered at the Ministry of Health hospitals from the beginning of November 1986 until the end of October 1988.

Two controls for each case were selected from women who did not have sickle cell disease or sickle cell trait. These controls were the first two women in the delivery register after the index patient who matched for parity and age (within one year). The mean age was 26·8 years (SD 5·85) in the index group and 26·7 years (SD 5·80) in the controls. In the index group there were 29 nulliparous women, 58 were parity 1 or 2, 27 were parity 3 or 4 and 33 were parity 5 and above. All the women with sickle cell disease were given a folic acid supplement in a dose of 5 mg thrice daily. An iron supplement was given only when indicated by a low serum iron level.

There were 147 deliveries in 140 women with sickle cell disease. These formed 0·8% of a total of 19 482 deliveries (Annual Statistical Report 1988). Of these 140 women, 127 had Hb-SS, 11 had Hb-S B Thal, one had Hb-SD and another had Hb-SO. We studied complications of pregnancy, perinatal and maternal mortality, and the use of blood transfusion. At the time the study was conducted, blood transfusions were given to pregnant women with sickle cell disease if their haemoglobin concentration was less than 10·0 g/dl.

The presence of HbS was determined by haemoglobin cellulose-acetate electrophoresis and fetal haemoglobin was estimated using the alkali-denaturation technique of Singer *et al* (1951). The amount of undenatured haemoglobin was measured photometrically using an Ilford No. 625 filter. The fetal haemoglobin percentage was calculated by the following equation:

$$\text{HbF\%} = \frac{\text{Optical density of the test}}{\text{Optical density of the standard}} \times 20$$

The normal range of HbF was considered to be from 0·2 to 4·0% (Singer *et al.* 1951).

Proformas for each woman with sickle cell disease and her pair of controls were completed and coded. The analysis was performed by calculating the relative risks (RR) and 95% confidence intervals (CI) using the statistical package CIA (Gardner *et al.* 1989).

Results

Description of complications

Complications during pregnancy were frequent. Overall 83 (56%) of the 147 pregnancies were complicated by sickle cell

---

Correspondence: Professor Affaf M. El-Shafei.

Table 1. Comparison of sickle cell disease pregnancies with and without crises

	With crises (*n* = 83) *n* (%)	Without crises (*n* = 64) *n* (%)	RR (95% CI)	χ^2 Trend
Age <25	38 (46)	19 (30)	1·0	4·8 (*P* = 0·03)
25–29	28 (34)	23 (36)	1·2 (0·9–1·7)	
>30	17 (20)	22 (34)	1·5 (1·0–2·3)	
Parity				
1	20 (24)	9 (14)	1·0	2·9 (*P* = 0·09)
2–4	39 (47)	30 (47)	1·2 (0·9–1·7)	
5+	24 (29)	25 (39)	1·4 (1·0–2·1)	
Anaemia	78 (94)	52 (81)	1·2 (1·0–2·1)	
Infection	3 (4)	0 —	—	
Hypertension	6 (7)	3 (5)	1·5 (0·4–5·9)	

crises. Of these 83 pregnancies, 61 (73%) had crises in the antenatal period, 7 (8%) in the postnatal period and 15 (18%) in both the antenatal and postnatal periods. In 46 (55%) pregnancies, the crises were of severe degree.

Anaemia was a common feature with sickle cell disease. In 130 of the 147 pregnancies (88%) the haemoglobin level was less than 10 g/dl. Of these, 80 (61%) had haemoglobin levels between 8·1 and 9·9 g/dl, 44 (34%) between 6·0 and 7·9 g/dl and 6 (5%) had a haemoglobin level less than 6 g/dl.

There were 150 babies born from the 147 deliveries, as the series included three sets of twins. The cord blood was analysed in 140 babies and was reported as sickle cell disease in 4, sickle cell trait in 37 and negative for sickling in 99. Six months later 127 babies were tested again. The blood results showed that 13 had sickle cell disease, 100 sickle cell trait and 14 were reported to be negative for sickling.

Characteristics of women who had crises

Of the 147 pregnancies in women with sickle cell disease 83 were complicated by crises. The women who developed crises were compared with those who did not suffer from this complication (Table 1). Relatively fewer crises occurred in older and women of higher parity, but the confidence limits for the relative risks show that this effect was statistically significant only for age (χ^2 for trend = 4·76, *P* = 0·03) and not for parity (χ^2 for trend = 2·87, *P* = 0·09).

The pregnancies in women with sickle cell crises were complicated more frequently by anaemia, infection and hypertension. For the latter two conditions it is difficult to draw any definite conclusion due to the small numbers involved.

Normal levels of HbF were found in 47 women and the rest had levels above 4%. It was noticed that fewer women suffered from crises when they had HbF levels above this value as shown in Table 2, but this difference was not statistically significant. However, HbF levels higher than 15% did reduce the severity of crises significantly (RR = 5·36, 95% CI 0·8–36·7).

Blood transfusions for anaemia and sickle cell crises were required in 109 pregnancies (74%); 81% of those with normal HbF required blood transfusion compared with 71% of those with raised HbF. Within 9 days of blood transfusion, 32 (39%) of the 83 patients who had been transfused for anaemia had severe crises without any other obvious precipitating factors. Of these, 18 (56%) had a crisis within 24 h, 10 (31%) within 72 h, and 4 (13%) between 72 h and 9 days after transfusion. On the whole, women with crises required more blood transfusions, 85% *vs* 44% in those without crises (*P*<0·02).

Comparison of cases with controls

The maternal and fetal complications in sickle cell disease women and controls were studied and are shown in Table 3. A significantly higher number of women with sickle cell disease were found to be anaemic and required greater number of blood transfusions. The frequency of hypertensive disorders of pregnancy, infections and diabetes were not found to be significantly different in those with sickle cell disease as compared to the controls. There were two maternal deaths in the women with sickle cell disease, equivalent to a maternal mortality rate of 1·4% but none in the controls.

Perinatal mortality was significantly higher in women with sickle cell disease; there were six stillbirths and five babies died in the early neonatal period from the total of 150 babies, giving a perinatal mortality rate of 73·3/1000 births *vs* 6·8/1000 births in the controls. Twenty-two babies (15%) were small for gestational age with a birthweight below the 10th centile (El-Shafei & Mostafa 1987) compared with 3% in the controls. The congenital abnormality rate of 5·3% was also found to be significantly higher in sickle cell disease compared with 1·4% in the controls.

The delivery statistics in the 147 pregnancies complicated by sickle cell disease are shown in Table 4. The preterm delivery rate was higher in those with sickle cell disease, compared to the controls. Thirteen (9%) had instrumental vaginal deliveries and 12% had caesarean section compared with 3% and 5% respectively, in the controls.

The indications for operative interference in sickle cell

Table 2. Relation of crises to level of HbF

	Crises (*n* = 83)		No crises (*n* = 64)				With severe crises (*n* = 46)		Without severe crises (*n* = 101)			
HbF	*n*	(%)	*n*	(%)	RR (95% CI)		*n*	(%)	*n*	(%)	RR (95% CI)	
Normal	29	(35)	18	(28)	1·00		18	(39)	29	(29)	1·00	
4·1–10%	32	(39)	25	(39)	1·1	(0·8–1·5)	20	(44)	37	(37)	1·1	(0·7–1·8)
10·1–15%	16	(19)	13	(20)	1·1	(0·8–1·7)						
>15%	6	(7)	8	(13)	1·4	(0·8–2·8)*	8	(17)	35	(35)	2·1	(1·0–4·2)**

*χ^2 for trend 1·4 (*P* = 0·24); **χ^2 for trend 5·21 (*P* = 0·02)

Table 3. Comparison of the maternal and fetal complications in patients with sickle cell disease and controls

Complication	SCD (147) *n* (%)	Controls (294) *n*(%)	RR (95% CI)
Anaemia	130 (88)	59 (20)	4·4 (3·5– 5·6)
Transfusion	109 (47)	11 (4)	19·8 (11·0–35·7)
PIH	10 (7)	18 (6)	1·1 (0·5– 2·4)
Infections	3 (2)	1 (–)	6·0 (0·6–57·2)
Diabetes	4 (3)	8 (3)	1·0 (0·3– 3·3)
Mortality			
Maternal	2 (1)	0 (–)	–
Perinatal	11 (7)	2 (1)	11·0 (2·5–49·0)
SGA	22 (15)	10 (3)	4·4 (2·1– 9·1)
Congenital abnormality	8 (5)	4 (1)	4·0 (1·2–13·1)

SCD: sickle cell disease.
SGA: small for gestational age.
PIH: pregnancy-induced hypertension.

disease women and controls were fetal distress (67% and 38%), cephalopelvic disproportion (10% and 20%), previous two caesarean sections (10% and 7%) and miscellaneous (13% and 35%) respectively.

There was an equal frequency of consanguinity in both the sickle cell disease women and controls (32%).

Discussion

Pregnancy in a women with sickle cell disease was hazardous for both the mother and baby. The intensity and frequency of the crises were more pronounced during pregnancy. More than half the women suffered from sickle cell crises, the majority during the antenatal period. In 55% the crisis was of a severe degree.

Considering the hazards of sickle cell disease during pregnancy, one would expect every subsequent pregnancy to carry a higher risk, as also mentioned by Harrison (1982b). In our study there was a suggestion that the primigravidae were at a greater risk than the parous women although the results were not statistically significant. However, women in the younger age group were at a significantly higher risk of having crises than the older women. A further investigation is needed to find out whether it is the younger age which is a risk factor or the primigravidae appear to be at greater risk because those with severe crises avoid further pregnancies or because they seek medical attention earlier and more frequently.

Anaemia is one of the major complications of sickle cell disease and may be due to haemolysis or trapping of the red blood cells in the spleen. All the women with sickle cell disease were given folic acid supplements. An iron supplement was not given unless indicated after investigation. In spite of this prophylactic treatment, nearly 90% of the women under study had a haemoglobin level less than 10·0 g/dl. Most of sickle cell disease women have chronic anaemia due to haemolysis, and tolerate this quite well. Rarely, life threatening anaemia may occur due to transient marrow aplasia resulting from viral infection or, to massive sequestration of sickled erythrocytes in the spleen (Hatton *et al.* 1985). We found that raised HbF levels did not decrease the number but reduced the severity of the crises. We also found that the pretransfusion levels of haemoglobin did not bear any relation to the frequency of the crises.

The greatest uncertainty over management policy for pregnancies in women with sickle cell disease hinges on the use of blood transfusion (Perrine & John 1974; Harrison 1982a). Some authors have failed to show any significant difference in the outcome of the pregnancy and others have considered that blood transfusion may increase risks (Morrison & Wiser 1976; Tuck *et al* 1987; Barnes 1974; Harrison 1982b). In this regard, we have noted that prophylactic transfusion can be dangerous as in 39% of the asymptomatic transfused patients, this was followed within 9 days by moderate to severe crises which resulted in one maternal death. The crises were probably precipitated by a rise in the haematocrit leading to increased blood viscosity and obstruction of the microcirculation. This finding is similar to that reported by Morrison *et al.* (1976). Consequently, we suggest that transfusion should be reserved for those women whose haemoglobin concentrations fall below 6 g/dl and that they should be given only washed red blood cells. The distribution of the subgroups of Hb SS and other variants was similar with regard to the number and severity of crises, anaemia and the use of blood transfusion.

Our study showed that the frequency of pregnancy induced hypertension was no different from that in the controls. This finding is contrary to that reported in other studies (Tuck & Studd 1983; Harrison 1982b).

There is a great variation in the rates of maternal mortality quoted, ranging from 0 to 71%, the higher figure deriving from a Nigerian Series (Fullerton & Turner 1962). We had two maternal deaths, a maternal mortality of 1·4% which is similar to that reported by Poddar *et al.* (1986) from Jamaica. In fact, sickle cell disease is one of the leading causes of maternal mortality in Bahrain (El-Shafei *et al.* 1988b).

The majority of maternal deaths in women with sickle cell disease are either due to septicaemia and thromboembolic episodes or from cardiac failure following haemolytic crisis. One of the two maternal deaths was a 25-year-old woman, pregnant for the fourth time, who was delivered of a macerated fetus at 26 weeks gestation and developed hepatorenal failure and disseminated intravascular coagulation as a result of crises. The other was 28 years old and in her third pregnancy who died undelivered at 36 weeks gestation after severe haemolytic crises and pulmonary embolism following blood transfusion for anaemia.

A high perinatal mortality rate is associated with sickle cell disease (El Shafei *et al.* 1988c). Most fetal deaths are the result of low birthweight and intrapartum asphyxia probably due to chronic maternal anaemia and impairment of placental func-

Table 4. Frequency of abnormal delivery in pregnancies complicated by sickle cell disease and in normal controls

Type of delivery	Sickle cell disease (*n* = 147) *n* (%)	Controls (*n* = 294) *n* (%)	RR (95% CI)
Preterm	14 (10)	9 (3)	3·1 (1·4– 7·0)
Breech	12 (8)	5 (2)	4·8 (1·7–13·4)
Instrumental	13 (9)	10 (3)	2·6 (1·2– 5·8)
Caesarean section	17 (12)	16 (5)	2·1 (1·1– 4·1)

tion as a result of reduced perfusion. In our study perinatal mortality was 7·3%, which is lower than the rate of 12–28% quoted by Harrison (1982b), and 24·8% quoted by Podder *et al.* (1986) from Jamaica. However, this perinatal mortality rate of 7·3% in our sickle cell disease women is still very much higher than the 0·7% in the controls. There were almost an equal number of stillbirths and early neonatal deaths. Milner *et al.* (1980) have reported a similar frequency but with 80% of the deaths being intrauterine and only 20% neonatal deaths.

In this group of pregnant women with sickle cell disease the frequency of babies that were small for gestational age was four times that found in the controls. This observation is similar to that reported in various series, for example, Powers *et al.* (1986) reported a birthweight of <2500 g at term in 30–40% of babies born to women with HbSS. There was also a higher frequency of preterm deliveries in these women which probably contributed towards the increased perinatal mortality. We found it to be 9·4% in the sickle cell disease women compared with 3·1% in the controls. All the cases of intrauterine growth retardation, perinatal mortality and maternal mortality were from amongst the HbSS group probably because they comprised almost 90% of all the women with sickle cell disease.

The mode of delivery was recorded and it was noted that the caesarean section and operative vaginal delivery rates were much higher in this group than in the controls. This is most probably due ot an early onset of fetal distress in labour. A similar observation was made by Podder *et al.* (1986). It has been reported that some of the women with sickle cell disease may need caesarean sections for pelvic deformities (Harrison 1982b) but we found that the frequency of caesarean section for cephalo-pelvic disproportion was in fact half of that found in the controls.

Cord blood is not satisfactory for the assessment of neonatal sickle cell status as 99 were found to be negative for sickling compared with only 14 at the age of 6 months. This inaccuracy at birth is due to the presence of high levels of HbF. Those babies showing negative sickling at 6 months were all from the 13 mothers who had heterozygous sickle cell variants. However, one of these mothers did have a baby with sickle cell disease as her husband had sickle cell trait.

In conclusion, these high risk pregnancies should be seen frequently in specialist clinics where they can be provided with optimal care, and we have started such a clinic in Bahrain. Blood transfusion should be given with extreme caution and only women with haemoglobin levels of less than 6 g/dl should be transfused in the absence of any other complications.

Premarital genetic counselling can help to reduce the frequency of sickle cell disease in future. At the same time pre-pregnancy counselling will make the women aware of the high risks associated with this disease and thus encourage them to book early and seek regular antenatal care.

References

Barnes C. G. (1974) Medical *Disorders in Obstetric Practice,* 4th edn., Blackwell Scientific Publication, London, p. 216.

El-Shafei A. M., Rao P. S. S. & Sandhu A. K. (1988a) Pregnancy and sickle cell haemoglobinopathies in Bahrain. *Saudi Med J* **9,** 283–288

El-Shafei A. M., Sandhu, A. K. & Dhaliwal J. K. (1988b) Maternal mortality in Bahrain with special reference to sickle cell disease. *Aust N Z J Obstet Gynaecol* **28,** 41–44.

El-Shafei A. M., Sandhu A. K. & Dhaliwal J. K. (1988c) Perinatal mortality in Bahrain. *Aust N Z J Obstet Gynaecol* **28,** 293–298.

El-Shafei A. M. & Mostafa F. E. (1987) Birthweight and gestational age in Bahrain. *Bah Med Bull* 9(3), 123–129

Fullerton W T. & Turner A. C. (1962) Exchange transfusion in the treatment of severe anaemia in pregnancy *Lancet* **i,** 75–78.

Gardner M. J , Gardner S. B. & Winter P. D. (1989) *Confidence Interval Analysis (CIA) Microcomputer Program Manual.* British Medical Association London.

Harrison K. A (1982a) Malaria and sickle cell disease *Clin Obstet Gynaecol* **9,** 467–476.

Harrison K. A. (1982b) Sickle cell disease in pregnancy. In *Sickle cell disease. A Handbook for the General Clinician* (Fleming A. F., ed), Churchill Livingstone, London, pp. 92–93.

Hatton C. S. R., Bunch C. & Weatherall D. J (1985) Hepatic sequestration in sickle cell anaemia. *Br Med J* **290,** 744–745.

Milner P. F., Jones B R. & Dobler J. (1980) Outcome of pregnancy in sickle cell anaemia and sickle cell-haemoglobin C disease. *Am J Obstet Gynecol* **138,** 239–245.

Ministry of Health (1988) Department of Obstetrics and Gynaecology Annual Statistical Report for 1988, Bahrain.

Morrison J. C. & Wiser W. L. (1976) The use of prophylactic partial exchange transfusion in pregnancies associated with sickle cell haemoglobinopathies *Obstet Gynecol* **48,** 516–520.

Perrine R. P. & John P (1974) Pregnancy in sickle cell anaemia in a Caucasian group. *Am J Obstet Gynecol* **118,** 29–33.

Poddar D., Maude G. H., Plant M J , Scorer H. & Serjeant G. R. (1986) Pregnancy in Jamaican women with homozygous sickle cell disease. Fetal and maternal outcomes. *Br J Obstet Gynaecol* **93;** 727–732.

Powars D. R., Sandhu M., Niland-Weiss J., Johnson C., Bruce S & Manning P. R. (1986) Pregnancy in sickle cell disease. *Obstet Gynecol* **67,** 217–228

Singer K., Chernoff A. & Singer L. (1951) Studies in abnormal haemoglobins. Their demonstration in sickle cell anaemia and other haematologic disorders by means of alkali denaturation. *Blood* **6,** 413–416

Tuck S. & Studd J. (1983) Obstetric problems of the black community. In *Progress in Obstetrics & Gynaecology* (Studd J , ed.) Vol. 3, Churchill Livingstone, London, pp. 17–33.

Tuck S. M , James C. E., Brewster E. M & Pearson T. C. (1987) Prophylactic blood transfusion in maternal sickle cell syndromes *Br J Obstet Gynaecol* **94,** 121–125.

Received 12 February 1990
Resubmitted 7 June 1991
Accepted 29 October 1991

British Journal of Obstetrics and Gynaecology
February 1992, Vol. 99, pp. 105–108

OBSTETRICS

Differences between obstetricians in caesarean section rates and the management of labour

JULIE GUILLEMETTE
WILLIAM D. FRASER

Department of Obstetrics and Gynaecology, Université Laval, Québec, Canada

ABSTRACT

Objective To determine if interobstetrician variation in caesarean section rates was associated with different approaches to the management of labour.

Design A retrospective cohort study.

Setting A tertiary care teaching hospital in Quebec, Canada.

Subjects 546 nulliparae in spontaneous labour at term were grouped according to the rate of caesarean sections for dystocia of their obstetrician (high: women of two obstetricians with rates of 13·2% and 15·0%; and low: women of three obstetricians with rates of 6·0%, 6·2% and 6·5%).

Main outcome measures Frequency and timing of oxytocin, epidural, amniotomy, forceps.

Secondary outcome measures Indicators of neonatal asphyxia and trauma.

Results No difference between groups was observed in the frequency or timing of use of oxytocin or epidural analgesia. Amniotomy was practised earlier by the obstetricians in the high group. Differences in section rates for dystocia were greatest in the second stage (low—2·4%, high—7·9%). Obstetricians in the low group intervened earlier with forceps or vacuum extractor. Nine babies (all in the low group), 8 of whom had had an instrumental vaginal delivery, suffered trauma (5 clavicular fractures, 4 facial palsies) (Fisher's exact test, $P = 0{\cdot}0139$).

Conclusion The practice patterns of the two groups are distinguished by differences in management of the second stage. Although lower section rates were associated with an increase in mild neonatal trauma, this appears to have been mediated by the earlier use of forceps in this group.

Since the early 1970s the rate of a caesarean section for dystocia has more than tripled in North America. The single indication contributing the most to this increase is dystocia. Marked variations have been observed in the section rate for dystocia between regions, hospitals, and among physicians working in the same hospital (Anderson & Lomas 1984; Goyert *et al.* 1989). The evidence that the liberal use of a caesarean section for dystocia has a beneficial effect on neonatal outcome in the term infant is limited (Fraser *et al.* 1988; Stembera 1987).

It has been observed that the practice-style of the delivery obstetrician is a major determinant of the likelihood of caesarean section. In a US study (Goyert *et al.* 1989), the range in personal rates of primary caesarean section for obstetricians working in one hospital was from 9·6% to 31·8%. Among the several risk factors assessed in that study, the only one with a greater effect on the likelihood of caesarean section than the 'obstetrician factor' was parity.

It has been suggested that an active approach to the medical management of labour, including early use of oxytocin and amniotomy, minimize the section rate for dystocia (O'Driscoll *et al.* 1984). Epidural anaesthesia has also been suggested as a factor that increases the section rate (Thorp *et al.* 1989). The purpose of our study was to determine whether there was an association between the obstetricians' management of labour, including the frequency and timing of the use of oxytocin, amniotomy, epidural anaesthesia and forceps, and his or her personal rate of caesarean section for dystocia.

Subjects and methods

The study was carried out at St-François d'Assise Hospital, a tertiary care teaching centre associated with Laval University in Quebec City, Canada. Women were included in the study if they were admitted between 1 April 1988 and 31 March 1990 and met the following criteria: nullipara, singleton pregnancy, term (≥37 weeks gestation), spontaneous labour with cephalic presentation, and intrapartum management by a specialist performing at least 100 deliveries during the study period. Women who were transferred from another hospital or who were referred intrapartum from a general practitioner to a specialist were excluded. In this centre, obstetricians participate in a shared on-call arrangement and the obstetrician who cares for women in spontaneous labour is determined solely by the day of birth.

Women were grouped according to the personal section rate for dystocia of their delivery-obstetrician, which was deter-

Correspondence: William Fraser MD., Département de Périnatologie, Local D0-705, Hôpital St-François d'Assise, 10, rue de l'Espinay, Québec (Québec) G1L 3L5, Canada

Table 1. Caesarean section rates (all indications and for dystocia) by obstetrician and by study group

		Caesarean section			
	Nulliparae	All indications		Dystocia only	
Obstetrician	*n*	*n*	(%)	*n*	(%)
Low group					
1	125	13	(10·4)	8	(6·4)
2	107	12	(11·2)	7	6·5)
3	100	7	(7·0)	6	(6·0)
High group					
4	114	19	(16·7)	15	(13·2)
5	100	22	(22·0)	15	(15·0)
Total	546	73	(13·5)	51	(9·4)

mined from the hospital's computerized perinatal database. The indication for the section was coded in the database using the diagnosis specified on the discharge summary sheet. The following diagnoses were included as dystocia: cephalopelvic disproportion, failure to progress in labour and failed forceps or vacuum extraction.

Initially, three groups were defined. The first group (low) was composed of women delivered by three obstetricians with section rates for dystocia of 6·0%, 6·2% and 6·5% (overall rate—6·3%). The second group (high) included women delivered by two obstetricians with section rates for dystocia of 13·2% and 15·0% (overall rate—14·0%). A third group included women delivered by an obstetrician whose personal section rate for dystocia was 10·3% but these women were excluded to facilitate comparison between high and low groups. A total of 546 women met the eligibility criteria (Table 1).

Obstetric and neonatal data were abstracted from two sources—patients' charts and the hospital's computerized database. The following data were abstracted from the charts: maternal age, febrile morbidity, number of days in hospital, the timing of onset of regular uterine contractions occurring at intervals of 5 min or less, arrival at hospital, first dose of epidural anaesthesia, narcotics, oxytocin, rupture of membranes, full dilatation and delivery. The following information was obtained from the hospital database: gestational age, smoking status, fetal monitoring during labour, perineal trauma, birthweight, Apgar scores at 1 and 5 min, method of neonatal resuscitation, umbilical vein blood pH, admission to neonatal intensive care, need for mechanical ventilation after transfer from the delivery room, administration of systemic antibiotics and vital status at hospital discharge.

Table 2. Characteristics of the women and their babies in the two study groups

Variables	Low group (*n* = 332)		High group (*n* = 214)	
Age (years)	25·7	4·6	25 8	(4·3)
Gestational age (days)	227 7	(8·4)	278·3	(7·8)
Prepregnancy weight (kg)	57·3	(10·0)	58·3	(10·4)
Weight gain (kg)	14·4	(4·9)	14·4	(4·7)
Birthweight (g)	3324·9	(423·6)	3391·6	(440·4)

Results are mean (SD) values.

Table 3. Distribution of methods of delivery by study group

Mode of delivery	Low group (*n* = 332)		High group (*n* = 214)	
Vaginal				
Spontaneous	144	(43·4)	83	(38·8)
Vacuum or low forceps	106	(31·9)	67	(31·3)
Vacuum and low forceps	20	(6·0)	10	(4·7)
Midforceps with rotation	10	(3·0)	3	(1·4)
Midforceps without rotation	20	(6·0)	10	(4·7)
Total vaginal	300	(90 3)	173	(80·9)
Caesarean section				
Dystocia—1st stage	13	(3·9)	13	(6·1)
—2nd stage	8	(2·4)	17	(7·9)*
Fetal distress	10	(3·0)	10	(4 7)
Other	1	(0·3)	1	(0·5)
Total sections	32	(9.6)	41	(19·2)
Total deliveries	332	(99·9)	214	(100 1)

Results are *n* (%) values.

*Significance of difference between the two groups χ^2 = 9·122, *P* = 0·0025.

The statistical significance of differences in proportions was assessed using the χ^2 and Fisher's exact tests. Student's *t*-test (pooled variance) was used to assess the statistical significance of differences between groups for continuous variables.

Results

Maternal and neonatal characteristics are shown in Table 2. The proportion of smokers was comparable in the two groups (low, 36·7% *vs* high, 36·9%). Cervical dilatation at admission was similar in the two groups (low: mean 2·7, SD 1·7 cm *vs* high: mean 2·3, SD 1·7 cm) and a similar proportion of women had intact membranes at admission (low, 68·4% *vs* high, 70·6%).

The distribution of women according to the delivery method is shown in Table 3. Nearly 60% of the difference between groups in section rates is explained by second stage sections for dystocia. The proportion of sections for dystocia which were performed with a cervical dilatation of ≤5 cm was similar in the two groups (low, 33·3% *vs* high, 26·7%).

The patterns of medical interventions in the two groups (narcotics, amniotomy, epidural anaesthesia and oxytocin) are shown according to their percentage use, timing of administration (Table 4), and cervical dilatation at the time of the intervention (Table 5). The only statistically significant difference

Table 4. Percentage use of medical intervention and mean interval from admission to intervention by study group

	Admission-intervention interval (min)					
	Low group (*n* = 332)			High group (*n* = 214)		
Interventions	% use	Mean	(SD)	% use	Mean	(SD)
Narcotics	13·3	401	(213)	11·7	427	(297)
Amniotomy	52·7	283	(230)	52·8	227	(196)*
Epidural	76·5	403	(274)	82·2	384	(263)
Oxytocin	49·7	465	(256)	56·1	429	(244)

**t* = −2·17, *P* = 0·031

Table 5. Cervical dilatation before the intervention by study group

Intervention	Cervical dilatation (cm) Low group (*n* = 322)	High group (*n* = 214)	*P*-value
Narcotics	3·1 (1·4)	3·0 (1·1)	0·82
Amniotomy	4·9 (2·4)	4·9 (2·7)	0·93
Epidural	6·1 (2·0)	6·1 (2·0)	0·92
Oxytocin	6·9 (2·9)	6·7 (3·1)	0·72
Caesarean section			
All indications	7·1 (2·7)	7·5 (3·1)	0·54
Dystocia	7·3 (2·8)	8·1 (2·7)	0·35

Results are mean (SD) values.

between groups was the timing of amniotomy which was performed, on average, nearly one hour earlier in the high group.

The mean duration of the interval from admission to delivery, and the mean durations of the first and second stages of labour for vaginal deliveries are shown in Table 6. The interval from admission to caesarean section was similar in the two study groups, whether all indications for section were considered, or only dystocia. When section for dystocia was performed after full dilatation, the duration of the second stage before delivery was similar in the two groups (low, 204 min *vs* high, 201 min).

For women delivered vaginally, the mean duration of the second stage of labour was significantly shorter in the low group. When only women experiencing spontaneous vaginal delivery were considered, the duration of the second stage was similar in the two study groups. However, for women having an operative vaginal delivery, the mean duration of the second stage was 20 min shorter in the low group than in the high group (*P* = 0·004) (Table 6).

The proportion of women with intrapartum (low, 0·9% *vs* high, 0·5%) and postpartum (low, 2·1% *vs* high, 2·3%) febrile morbidity (>38°C) was similar in the two study groups. The proportion with 3rd or 4th degree perineal tears was also similar in the two groups (low, 10·5% *vs* high, 14·5%). The mean duration of hospital admission was shorter in the low group than in the high group (low, mean 4·7 SD, 1·7 days *vs* high, mean 5·3, SD 3·3 days).

Table 6. Mean interval from admission to delivery and duration of labour in the two study groups

	Low Group (*n* = 332)	High group (*n* = 214)	Significance *t*	*P*
Admission to delivery interval (min)				
All women	532 (321)	549 (307)		
Caesarean sections				
All indications	745 (515)	748 (365)		
Dystocia	921 (536)	859 (336)		
Duration of labour (min) (vaginal births)				
First stage*	433 (276)	407 (253)		
Second stage†				
All vaginal births	79 (45)	92 (53)	2·71	0·006
Spontaneous delivery	63 (38)	69 (38)		
Operative delivery	93 (46)	112 (58)	2·91	0·004

Results are mean (SD) values

*Admission to full dilatation.

†Full dilatation to delivery.

Electronic fetal monitoring was used with similar frequency in the two study groups (low, 81·6% *vs* high, 85·5%). Indicators of neonatal status are shown on Table 7. The single perinatal loss was a neonatal death secondary to feto-maternal haemorrhage. There was no difference between the two groups in the frequency of convulsions, abnormal cerebral signs or meconium aspiration syndrome. The proportion of babies with Apgar scores <6 at 1 min and <8 at 5 min was similar in the two groups.

Nine babies were affected by trauma (5 clavicular fractures, 4 facial palsies). All these babies were born in the low group (Fisher's exact test; *P* = 0·0139). Eight of these nine births were by forceps or vacuum extraction.

Discussion

In the present study, although the number of obstetricians studied was small, distinctive approaches to the management of labour were identified. Differences between groups in the overall rate of caesarean were primarily the result of the method of management of the second stage of labour. However, obstetricians in the high group also performed sections for dystocia more frequently in the first stage. Additionally, section for fetal distress was more frequent in the high group. Taken together, the result was a twofold difference in section rates.

Although differences between groups in the frequency and timing of oxytocin and epidural anaesthesia had been expected, no statistically significant differences were observed. Paradoxically, amniotomy, which is usually intended to facilitate labour progress, was performed earlier in the high group.

In some hospitals, a significant proportion of sections for dystocia are performed during the latest phase of labour (Stewart *et al.* 1990). Such was the case in the current study, where nearly one-third of sections for dystocia were performed with a

Table 7. Neonatal outcome by study group

Outcome	Low group (*n* = 332) *n* (%)	High group (*n* = 214) *n* (%)
Perinatal death	0 (—)	1 (0·5)
Apgar score		
<6 at 1 min	7 (2·1)	10 (4·7)
<8 at 5 min	2 (0·6)	2 (0·9)
Umbilical vein pH <7·20†	3 (0·9)	2 (0·9)
Admission to NICU	19 (5·7)	11 (5·1)
Endotracheal intubation	1 (0·3)	1 (0·5)
Abnormal cerebral signs	1 (0·3)	1 (0·5)
Meconium aspiration syndrome	4 (1·2)	2 (0·9)
Clavicular fracture	5 (1·5)	0 (—)*
Facial palsy	4 (1·2)	0 (—)*

NICU = Neonatal intensive care unit.

*Fisher's exact *P*-value = 0·0139 for combined trauma events.

†There were 45 values missing in the low group and 48 values in the high group.

cervical dilatation of 5 cm or less. However, differences between groups in overall sections rates could not be accounted for on this basis.

The fact that the study was carried out in a teaching hospital where residents participate in decisions regarding the use of oxytocin and epidural may explain the relative homogeneity in the use of these interventions. Decisions regarding operative procedures, including operative vaginal deliveries and caesarean section are referred to the obstetric consultant. It was here that inter-obstetrician differences were most apparent.

It would appear that the obstetricians in the low group were more at ease with operative vaginal delivery than their colleagues in the high group. Complex operative vaginal procedures (forceps after failed vacuum, midforceps with and without rotation) were performed more frequently in the low group, although these differences were not statistically significant. More notably, obstetricians in the low group applied forceps and vacuum nearly 20 mins earlier than their colleagues in the high group.

On average, obstetricians in both groups observed the second stage for more than 3 h before performing caesarean section for dystocia. This indicates that the degree of delay necessary to justify a section was similar in the two groups.

In the present study, the benefits associated with a lower section rate came at the cost of an increase in mild forms of neonatal trauma. Clavicular fractures are almost always benign (Joseph *et al.* 1990). Facial palsies are usually associated with midforceps delivery (Cyr *et al.* 1984) and the great majority resolve without lasting sequelae. It would seem possible that the benefits of a low section rate could be maintained while minimizing the risk of trauma by more judicious timing of operative vaginal delivery. Mean second stage duration before operative vaginal delivery was, in both groups, shorter than the traditionally suggested 2 h.

In summary, this study indicates that marked obstetrician variation in section rates may occur despite similarities in the use of oxytocin and epidural. Earlier use of amniotomy was associated with a higher section rate. If second stage section rates are to be reduced safely, careful attention must be given to the frequency, and particularly the timing of operative vaginal delivery.

Acknowledgment

Dr Fraser receives salary support through a Medical Research Council of Canada Development Grant.

References

Anderson G. M. & Lomas J. (1984) Determinants of the increasing caesarean birth rate. *N Engl J Med* **311**, 887-892.

Cyr R. M., Usher R. H. & McLean F. H. (1984) Changing patterns of birth asphyxia and trauma over 20 years. *Am J Obstet Gynecol* **148**, 490-498

Fraser W. D., Usher R. H., McLean F. *et al.* (1988) Conservative rate of caesarean section for dystocia: A risk factor for neonatal asphyxia and trauma? Abstract presented at the Annual Meeting of the Society of Perinatal Obstetricians, Las Vegas, 1988.

Goyert G. L., Bottoms S. F, Treadwell M. C. & Nehra P. C. (1989) The physician factor in caesarean birth rates. *N Engl J Med* **320**, 706-709.

Joseph P. R. & Rosenfeld W. (1990) Clavicular fractures in neonates. *Amer J Disease Child* **144**, 165-167.

O'Driscoll K., Foley M. & MacDonald D. (1984) Active management of labour as an alternative to caesarean section for dystocia. *Obstet Gynecol* **63**, 485-490.

Stembera Z. (1987) Unpublished data cited in Lomas J. & Enkin M (1989) Variations on operative delivery rates. In *Effective Care in Pregnancy and Childbirth* (Chalmers I., Enkin M. & Keirse M. J. N. C., eds), Oxford University Press, Oxford.

Stewart P. J., Dulberg C., Arnill A. C., Elmslie T. & Hall P. F. (1990) Diagnosis of dystocia and management with caesarean section among primiparous women in Ottawa-Carleton. *Can Med Assoc J* **142(5)**, 459-463.

Thorp J. A., Parisi V M., Boylan P C. & Johnston D. A. (1989) The effect of continuous epidural analgesia on caesarean section for dystocia in nulliparous women. *Am J Obstet Gynecol* **161**, 670-675.

Received 3 May 1991
Accepted 7 October 1991.

British Journal of Obstetrics and Gynaecology
February 1992, Vol. 99, pp. 109–111

OBSTETRICS

The treatment of intrahepatic cholestasis of pregnancy by dexamethasone

MARJA-LIISA HIRVIOJA
RISTO TUIMALA
Department of Obstetrics and Gynecology
University of Tampere, Finland
JUHANI VUORI
Deaconess Institute of Oulu, Finland

ABSTRACT

Objective To investigate whether dexamethasone supression of fetoplacental oestrogen production can reduce obstetric cholestasis.
Design Observational study.
Setting Department of Obstetrics and Gynaecology, University of Tampere, Finland.
Subjects 10 women, at between 28 and 37 weeks gestation, with intrahepatic cholestasis of pregnancy.
Interventions Treatment with 12 mg oral dexamethasone daily for 7 days, after which the therapy was gradually discontinued over 3 days.
Main outcome measures Serum oestriol, oestradiol, total bile acids and ALAT were measured before and during therapy and on days 4 and 7 and ALAT also on day 12. Differences were tested by paired *t* test.
Results Itching disappeared or was relieved in all patients. Serum oestriol level fell significantly by day 1 of treatment, serum oestradiol and total bile acid levels by day 4 and ALAT by day 12 from the beginning of the therapy.
Conclusion Dexamethasone is a drug of choice in the treatment of intrahepatic colestasis of pregnancy.

In the Scandinavian countries the prevalence of intrahepatic cholestasis of pregnancy, the most common liver disorder during pregnancy, is 1–1·5% (Heikkinen 1982; Berg *et al.* 1986). This condition is characterized by intensive itching, elevated serum transaminase and bile acid levels and sometimes stillbirth, which is thought to be associated with high bile acid concentrations (Heikkinen 1982: Laatikainen & Ikonen 1975; Laatikainen & Ikonen 1977). The treatment of intrahepatic cholestasis has been in the main symptomatic, including phenobarbitone, cholestyramine and antihistamines, but no specific effective therapy has yet been found.

During pregnancy the main circulating oestrogen is oestriol and about 90% of the total amount is derived from the fetus and placenta. About 50% of the serum oestradiol comes from the fetoplacental unit. Fetal adrenals provide dehydroepiandrosterone (DHEAS) as a precursor for the placental production of oestrogens (Siiteri & MacDonald 1966; Madden *et al.* 1978). Dexamethasone penetrates the placenta and is known to reduce DHEAS secretion from fetal adrenals, resulting also in a reduction in oestrogen production (Simmer *et al.* 1974; Simmer *et al.* 1975; Kauppila *et al.* 1976; Kauppila *et al* 1979). In obstetric cholestasis increased circulating oestrogen concentrations associated with a normal pregnancy lead to intrahepatic cholestasis because of abnormal hepatic reactivity.

The aim of the present investigation was to establish whether the suppression of fetoplacental oestrogen production by dexamethasone treatment reduced obstetric cholestasis.

Correspondence: Risto Tuimala, Tayks, Teiskontie 35, SF-33520 Tampere, Finland.

Subjects and methods

Ten women, at between 28 and 37 weeks gestation, with intrahepatic cholestasis of pregnancy were involved in the study. They were given oral dexamethasone, 12 mg daily for 7 days, after which the therapy was gradually discontinued over 3 days.

Serum oestriol and oestradiol levels were determined before and on days 1, 4 and 7 of therapy. Serum total bile acids and serum alanine aminotransferase (ALAT) levels were measured before therapy and on days 4 and 7, ALAT was measured again 12 days after the beginning of therapy.

Venous blood samples were obtained at 08.00 h before breakfast. Serum ALAT, total bile acids and oestradiol were determined immediately, the samples for oestriol measurement were centrifugated and stored at −20°C.

Serum oestriol was determined with the total oestriol (^{125}I) RIA Kit test (Farmos, Oulunsalo, Finland), a radioimmunoassay for the quantitative measurement of total (free and conjugated) oestriol in human serum.

Serum oestradiol was measured with ^{125}I-oestradiol direct RIA Kit test (Baxter Dade AG, Dudingen, Switzerland), which is used for the direct quantitative determination of 17-β-oestradiol levels in serum and plasma, based on the competitive binding radioimmunoassay principles.

Serum total bile acids were determined with Enzabile test from Nycomed (Nycomed AS, Pharma, Oslo, Norway), an enzymatic, colorimetric determination method of total 3-a-hydroxy bile acids in serum, gastric juice and faeces.

Serum ALAT was determined using the standard automated ultraviolet kinetic method with the composition of reagents

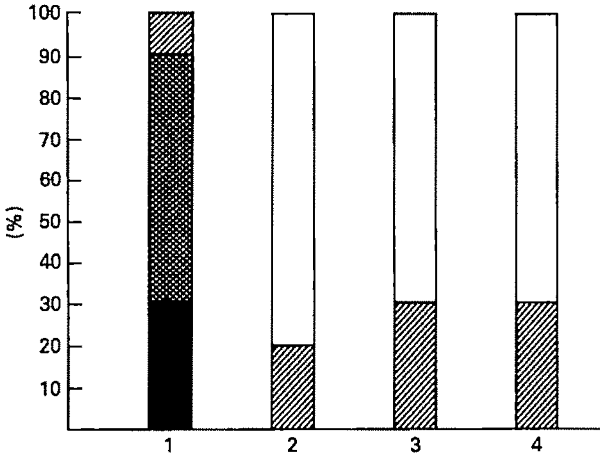


Fig. 1. Effect of dexamethasone on itching in 10 women with intrahepatic cholestasis of pregnancy. ■, severe itching; ▩, moderate itching; ▨, mild itching; □, no itching.
1. Before dexamethasone treatment; 2. day 3 of treatment; 3. day 7 of treatment; 4. 12 days after the start of treatment.

recommended by the Scandinavian Enzyme Committee (1974).

The patients were observed regularly, and the wellbeing of the fetus was checked by daily cardiotocography. The patients assessed the degree of itching daily. Differences were tested by paired *t*-test.

Results

Itching disappeared or was markedly relieved during dexamethasone treatment in all the patients (Fig. 1). Circulating oestriol levels fell significantly ($P<0{\cdot}01$) after the first day of therapy, oestradiol and total bile acid levels after 4 days therapy (Figs 2, 3). Serum ALAT values increased during the first 4 days of therapy but by day 12 after the start of treatment ALAT concentration was significantly lower ($P<0{\cdot}05$) than before therapy (Fig. 3). Symptoms of cholestasis did not recur after therapy, and all patients gave birth to a healthy child.

Discussion

The serum oestrogen-reducing effect of dexamethasone treatment is well known (Simmer *et al.* 1974; Simmer *et al.* 1975; Kauppila *et al.* 1976), and it was also shown in this study. Symptoms began to diappear soon after oestrogen levels fell. Although oestrogen levels are known to rise immediately after stopping treatment (Kauppila *et al.* 1976), the symptoms of cholestasis did not recur even in one of our patients who gave birth more than 2 months after stopping therapy. A possible explanation is that cholestasis takes a relatively long time to develop in pregnancy, oestrogen levels are high from the end of the first trimester but obstetric cholestasis usually appears only during the last few weeks of pregnancy.

Prenatal glucocorticoid therapy is widely used and in the prevention of neonatal respiratory distress syndrome, and no adverse effects on the fetus have been reported (Kauppila *et al.* 1976; Kauppila *et al.* 1978; Cederqvist *et al.* 1978; Kauppila *et al.* 1979; Huhtaniemi *et al* 1982). There are two risks for the fetus in obstetric cholestasis, unexplained stillbirth and a tendency to preterm labour (Laatikainen & Ikonen 1975; Fisk & Storey 1988). Dexamethasone treatment may lessen both risks in that stillbirth is probably associated with the high bile acid

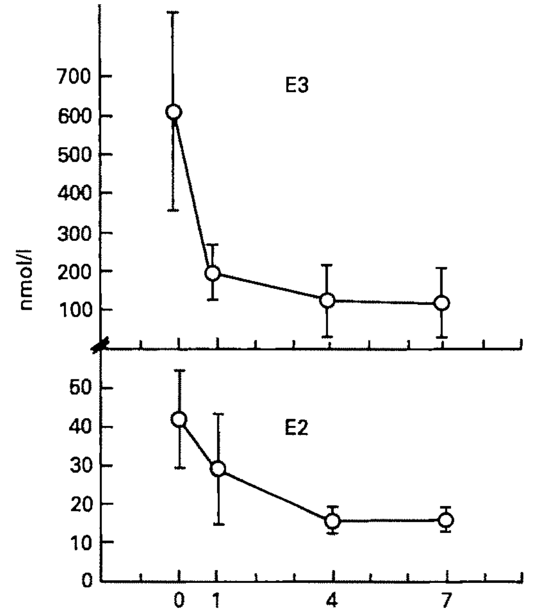


Fig. 2. Serum levels (mean ± SD) of oestriol (E_3) and oestradiol (E_2) before (day 0) and on days 1, 4 and 7 during 7 days of dexamethasone therapy in 10 women with intrahepatic cholestasis of pregnancy.

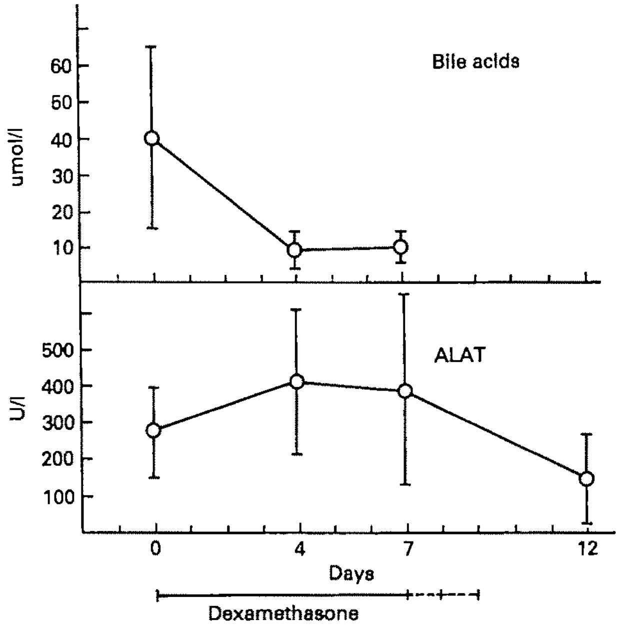


Fig. 3. Serum levels (mean ± SD) of alanine aminotransferase (ALAT) and total bile acids before (day 0) and on days 4 and 7 during 7 days of dexamethasone therapy in 10 women with intrahepatic cholestasis of pregnancy. ALAT levels were measured again 12 days after the start of treatment.

concentrations and these fell significantly during dexamethasone therapy and furthermore the fetal lung maturing effect of dexamethasone would present the neonatal respiratory distress syndrome if preterm birth occurred.

Patients suffering from intrahepatic cholestasis are often bothered by intensive itching that disturbs sleep. In this study dexamethasone reduced itching significantly in all pregnancies. Cholestyramine treatment has been shown to improve itching but cholestyramine is known to reduce absorption of vitamin K from the small intestine and may thus expose the patient to bleeding.

Glucocorticoids are known to increase insulin resistance. Although our study did not include any latent or manifest diabetics, we do not regard diabetes as an absolute contraindication to dexamethasone treatment, but diabetics may require increased insulin doses during therapy.

We found no fetal maternal side-effects with other therapies such as cholestyramine and phenobarbitone, dexamethasone treatment was more effective and better tolerated. We now regard it as a drug of choice in intrahepatic cholestasis of pregnancy. Because of the fluctuating nature of intrahepatic cholestasis and the small number of patients in the study, a more extensive, placebo-controlled investigation will be necessary to confirm the findings.

References

Berg B., Helm G., Petersohn L. & Tryding N. (1986) Cholestasis of pregnancy. Clinical and laboratory studies. *Acta Obstet Gynecol Scand* **65**, 107-113.

Cederqvist L. L., Ylikorkala O., Ekelund L., Tuimala R. & Litwin S. D. (1978) Fetal immunoglobulin production following prenatal glucocorticoid treatment. *Obstet Gynecol* **53**, 539-541.

Fisk N. M. & Storey G. N. B. (1988) Fetal outcome in obstetric cholestasis. *Br J Obstet Gynaecol* **95**, 1137-1143.

Heikkinen J. (1982) Bile acids in pregnancy. *Acta Univ Oul* D.89.

Huhtaniemi I., Koivisto M., Pakarinen A., Tuimala R. & Kauppila A. (1982) Pituitary-adrenal and testicular function in preterm infants after prenatal dexamethasone treatment. *Acta Paediatr Scand* 71, 425-429.

Kauppila A., Jouppila P., Karvonen P., Tuimala R. & Ylikorkala O. (1976) Effect of dexamethasone on blood levels of ACTH, cortisol, progesterone, estriol and estradiol during late pregnancy. *Int J Gynaecol Obstet* **14**, 177-181.

Kauppila A., Koivisto M., Puukka M & Tuimala R. (1978) Umbilical cord and neonatal cortisol levels. Effect of gestational and neonatal factors. *Obstet Gynecol* **52**, 666-672.

Kauppila A., Tuimala R., Ylikorkala O., Reinilä M. & Ylöstalo P. (1979) Placental steroid synthesis from DHEAS during dexamethasome therapy. *Obstet Gynecol* **54**, 39-41.

Laatikainen T. & Ikonen E. (1975) Fetal prognosis in obstetric hepatosis. *Ann Chir Gynecol* **64**, 115.

Laatikainen T. & Ikonen E. (1977) Serum bile acids in cholestasis of pregnancy. *Obstet Gynecol* **50**, 313.

Madden J. D., Gant N. F. & MacDonald P. C. (1978) Study of the kinetics of conversion of maternal plasma dehydroisoandrosterone sulfate to 16-a-hydroxydehydroisoandrosterone sulfate, estradiol and estriol. *Am J Obstet Gynecol* **132**, 392.

Siiteri P. K. & MacDonald P. C. (1966) Placental estrogen biosynthesis during human pregnancy. *J Clin Endocrinol Metab* **26**, 751.

Simmer H. H., Frankland M. & Greipel M. (1975) On the regulation of fetal and maternal 16-a-hydroxydehydroepiandrosterone and its sulphates by cortisol and ACTH in human pregnancy at term. *Am J Obstet Gynecol* **121**, 646-652.

Simmer H. H., Tulchinsky D., Gold E. M., Frankland M., Greipel M. & Gold A. S. (1974) On the regulation of estrogen production by cortisol and ACTH in human pregnancy at term. *Am J Obstet Gynecol* **119**, 283-295.

Received 20 May 1991
Accepted 24 October 1991

British Journal of Obstetrics and Gynaecology
February 1992, Vol. 99, pp. 112–117

OBSTETRICS

Role of prostaglandin in the management of prelabour rupture of the membranes at term

T. A. MAHMOOD
Senior Registrar
M. J. W. DICK
Registrar
N. C. Smith
Consultant
A. A. TEMPLETON
Professor
Department of Obstetrics and Gynaecology
Aberdeen Maternity Hospital
Cornhill Road, Aberdeen, UK

ABSTRACT

Objective To compare conservative *versus* prostaglandin management of prelabour rupture of the membranes (PROM) in healthy primigravid women at term.
Design A prospective randomized study.
Setting Labour Ward, Aberdeen Maternity Hospital.
Subjects 230 primigravidae at term with PROM, 115 allocated to be treated conservatively and 115 to be managed with prostaglandin treatment.
Interventions In the conservatively managed group the women were observed for up to 24 h after hospital admission with PROM. The actively managed group had PGE_2 gel (2 mg) instilled into the posterior fornix and if contractions had not commenced, a further dose of PGE_2 gel (1 mg) was instilled 6 h later. In both groups, if labour had not established 24 h after admission, intravenous oxytocin was given in escalating doses.
Main outcome measures PROM to delivery interval, oxytocin augmentation, mode of delivery, maternal and neonatal infective morbidity.
Results There was a significant reduction in the PROM to delivery interval in the women managed actively with PGE_2 gel and fewer women in the PGE_2 group required oxytocin augmentation (31% *vs* 51%). The two managements groups were comparable for intrapartum analgesia, antibiotic treatment, babies requiring admission to the special care nursery unit and delivery by caesarean section.
Conclusion The early use of prostaglandin is associated with a significant reduction in PROM to delivery interval without a significant increase in infective morbidity or caesarean section rate. However, the advantages of the conservative approach should not be overlooked. More work is still needed in the management of those women where uterine activity fails to establish within 24 h after PROM.

The management of prelabour rupture of the membranes (PROM) in healthy primigravidae at term (gestation ≥37 weeks) without uterine activity is a matter of debate. In most cases, labour ensues within 24 h (Duff *et al* 1984; Conway *et al.* 1984), but a delay between membrane rupture and delivery has been associated with an increased risk of sepsis and perinatal morbidity (Fayez *et al.* 1978; Yoder *et al.* 1983; Daikoku *et al.* 1982). There is, therefore, a tendency to induce labour with intravenous oxytocin or vaginal prostaglandins to lessen the risk of ascending intrauterine infection (Lange *et al.* 1981; Westergaard *et al.* 1983; Ekman-Ordeberg 1985). However, active management has been associated with a higher caesarean section rate (Duff *et al.* 1984; Morales & Lazar 1986), which may be related to an underlying dystocia caused by a deficiency in prostaglandin production or in prostanoid biosynthesis (Keirse *et al.* 1987). The hypothesis is supported by a few studies that compared prostaglandin with oxytocin for induction (Hauth *et al.* 1977; Lange *et al* 1981; Magos *et al.* 1983) and found a lower section rate associated with prostaglandins. On the other hand, Rovinsky & Shapiro (1968), Kappy *et al.* (1979, 1982) and O'Driscoll & Meagher (1980) recommend awaiting spontaneous onset of labour, especially in the presence of an unfavourable cervix, to decrease the need for caesarean section without increasing infective morbidity.

Some studies have been criticized for not being fully randomized trials (Duff *et al.* 1984; Morales & Lazar 1986) and the three studies by (Hauth *et al* (1977); Lange *et al* (1981) and Magos *et al.* (1983) for not including a third study arm dealing with conservative management. We designed a prospective study to test the hypothesis that treatment with prostaglandin (PG) E_2 gel would halve the PROM to delivery interval without increasing the frequency of caesarean section or of infective morbidity.

Subjects and methods

Trial design

The case notes were reviewed of 100 consecutive primigravidae with PROM at term who were managed conservatively in Aberdeen Maternity Hospital during 1986. The

Correspondence: Dr T. A. Mahmood, Consultant Obstetrician & Gynaecologist, Forth Park Hospital, 30 Bennochy Road, Kirkcaldy, Fife KY2 5RA, Scotland, UK.

Table 1. General characteristics of the two study groups

Variable	Conservative group (n = 110)		PGE$_2$ group (n = 110)	
Age (years)	25·8	(0·40)	26·3	(0·46)
Height (cm)	161	(0·60)	160	(0·60)
Marital status				
Married	87	(79)	93	(85)
Single	22	(20)	15	(14)
Divorced/separated	1	(1)	2	(1)
Gestational age at PROM (days)	277	(10)	275	(9)
Birthweight (kg)	3·44	(0·23)	3·37	(0·30)
Position of the presenting part				
Occipito posterior	23	(21)	23	(21)
Occipito transverse	35	(32)	36	(33)
Occipito anterior	49	(45)	45	(41)
Not stated	3	(2)	6	(5)
Analgesic requirement				
Pethidine/Diamorphine	73	(66)	68	(62)
Epidural	32	(29)	33	(30)
Entonox	2	(2)	5	(4·5)
No analgesia	3	(3)	4	(3 5)
Endocervical swab at entry				
β-haemolytic streptococci	8	(7)	8	(7)
Candida	2	(2)	2	(2)
Gardnerella vaginalis	1	(1)	1	(1)
Others	3	(3)	2	(2)

Results are mean (SD) or n (%) values as appropriate.
There were no significant differences between the two groups.

mean time interval between hospital admission to delivery was 32 h (range 12–60 h). Using Pocock's formula (α = 0·05 and β = 0·20, power 0·80), 220 subjects (110 in each study arm) would be required to test the hypothesis that treatment with PGE$_2$ gel (to prime the cervix) would reduce the PROM to delivery interval by 50% without increasing the frequency of caesarean section. A further 10 women (5 in each arm) should be recruited to account for protocol violations in the trial. The study proceeded between January 1988 and May 1990.

Study groups

Only primigravid women with PROM in a singleton pregnancy of certain gestation (confirmed by early pregnancy ultrasound) and cephalic presentation, with no uterine activity were eligible for inclusion. In addition, women with previous significant antepartum haemorrhage, intrauterine growth retardation, diabetes mellitus, Rhesus disease, moderate pre-eclampsia, a history of venereal disease, a temperature >37·5°C on admission, ruptured membranes for >12 h or meconium stained amniotic fluid on admission were excluded.

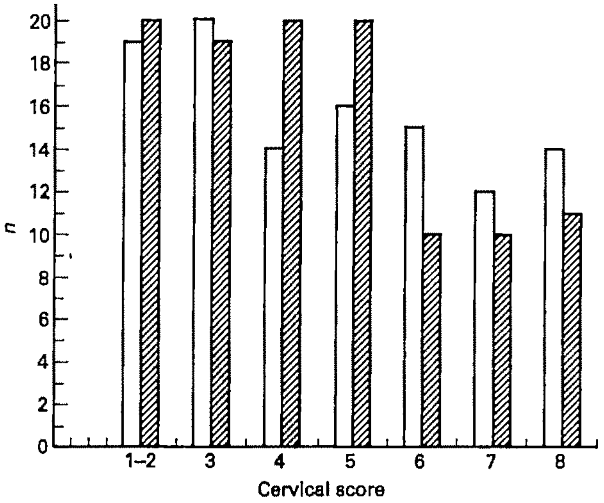


Fig. 1. Comparison of cervical score at randomization in the two management groups ☐ conservative management, ▨ active management with PGE$_2$ gel.

The diagnosis of PROM was confirmed by a sterile speculum examination to demonstrate the presence of amniotic fluid in the posterior fornix. An endocervical swab was taken and sent in Stuart's transport medium for urgent microscopy, culture and sensitivity. The results of microscopy were available within 2 h. This was followed by a sterile digital examination to exclude occult cord prolapse and to assess cervical score (Calder *et al.* 1974). All women in both groups had a cervical dilatation <3 cm at entry to the trial. An external cardiotocographic tracing (CTG) was recorded for 30 min. The women were given an information sheet and written consent was obtained. Once the patient had consented to enter the study, a numbered sealed randomization envelope was opened which allocated her to one of the two study groups.

Management

The 115 women randomized to conservative management remained for up to 24 h in the observation ward. They had their

Table 2. Details of labour and postpartum in the two study groups

Variable	Conservative group (n = 110)		PGE$_2$ group (n = 110)		Difference	(95% CI)
No. of vaginal examinations	4·24	(1·63)	4·21	(1·65)	0·03	(−0·40 to 0·46)
Intrapartum pyrexia	21	(19)	19	(17)	2%	(−7·0 to 12)
Intrapartum meconium	12	(11)	7	(6)	5%	(−10·0 to 20)
Antibiotics given	17	(15·5)	14	(13)	3%	(−7·0 to 11)
Postpartum pyrexia	15	(14)	4	(4)	11%	(2·5 to 17)*
Primary postpartum haemorrhage	4	(4)	3	(3)	1%	(−14 to 16)

*P<0·05.
Results are mean (SD) or n (%) values as appropriate.

Table 3. Indications for maternal antibiotic treatment in the two study groups

Indication	Conservative group	PGE_2 group
β-haemolytic streptococci at initial endocervical swab	8	8
Intrapartum pyrexia	5	4
Postpartum urinary tract infection	4	2
Total	17	14

blood pressure, pulse and temperature checked every 6 h. If labour did not ensue after 24 h they were treated with intravenous oxytocin using an escalating scale of 1–32 mU/min.

The other 115 women randomized to active management had PGE_2 gel (2 mg) (Upjohn) instilled into the posterior fornix. An external cardiotocogram (CTG) was recorded for 1 h. If uterine activity did not ensue, then a repeat treatment with PGE_2 gel (1 mg) was given 6 h later.

In both groups intravenous oxytocin was started 24 h after hospital admission, if labour had not begun or sooner if augmentation of established labour was required.

During labour, intravenous oxytocin in an escalating dose was given according to normal practice when a diagnosis of inefficient uterine activity was made (two mild to moderate uterine contractions in 10 min, lasting <30 s). Intravenous oxytocin infusion was also used in the absence of any further cervical dilatation at subsequent vaginal assessment 4 h later or if there was a delay in second stage.

In labour, continuous electronic fetal heart monitoring was undertaken. Epidural analgesia was available on demand. The women were coded as pyrexial if maternal temperature exceeded 37.5°C in labour or within 24 h after delivery.

Each newborn was seen and examined by a paediatric resident, who was unaware of the woman's participation in the study.

All data were collected by one of the authors (M.J.W.D.) This trial was approved by the joint Ethics Committee of Grampian Health Board and the University of Aberdeen. Data were analysed on Minitab statistical package (Statistics Dept, Pennsylvania University) using the *t* test, χ^2 or Fisher's exact test, Mann–Whitney *U* test and 95% confidence intervals (CI) where appropriate.

Results

Of the 230 women randomized, ten were excluded from the final analysis (five in each group) because they did not fulfil the study criteria (four with undiagnosed breech presentation; two who were parous; two had had a positive nitrazine test at randomization but without a definite fluid pool in the vagina and two whose case notes could not be traced). This analysis is based on 220 women.

General characteristics of the study groups

The two groups wre comparable in terms of age, height, marital status, gestation at PROM, birthweight, position of the presenting part in labour, requirement for intrapartum analgesia and the proportion with a positive endocervical swab at entry (Table 1). Similarly, cervical scores at randomization were comparable in the two groups (Fig. 1).

Requirement for prostaglandins E_2

Of the 110 women managed with PGE_2, 71 (65%) required only one dose of PGE_2 gel (2 mg) and the remaining 39 (35%) had a second dose of 1 mg 6 h later. None required a third dose.

Characteristics of labour

There was no difference between the two groups in the mean number of vaginal examinations in labour and in the proportions developing intrapartum pyrexia or intrapartum meconium (Table 2). A similar proportion of women in each group were given antibiotic treatment for the indications shown in Table 3. All women with a positive endocervical swab for β haemolytic streptococci at entry were treated prophylactically with antibiotics. Similarly, other women with intrapartum pyrexia (with a negative cervical swab) were also treated with prophylactic antibiotics.

Sustained postpartum pyrexia (>37·5°C lasting longer than 48 h) occurred in a higher proportion of women in the conservative group. A similar proportion of women in the two groups experienced significant primary postpartum haemorrhage (Table 2).

Oxytocin augmentation and outcome of labour (Table 4)

There was no evidence of uterine activity 24 h after PROM in

Table 4. Outcome of labour in the two study groups

Variable	Conservative group (*n* = 110)	PGE_2 group (*n* — 110)	Difference	(95% CI)
Oxytocin augmentation *n* (%)	56 (51)	34 (31)	22%	(9 to 34)*
Interval from PROM to				
Onset of uterine activity (h) mean (SD)	17·88 (12·46)	5·47 (4 78)	12	(9·94 to 14·87)*
Start of oxytocin augmentation (h) mean (SD)	26·24 (5·75)	17·04 (4·99)	9	(6·82 to 11·59)*
	(*n* = 56)	(*n* = 34)	9	
Delivery (h) mean (SD)	26·88 (8·90)	20·05 (6·55)	6·8	(4·77 to 8·88)*
median (range)	23·50 (6–53)	19·00 (4–39)		
Duration of second stage (min) mean (SD)	100 (62)	86 (68)	14	(10 to 18)

PROM = prelabour rupture of membranes.
*$P<0·001$.

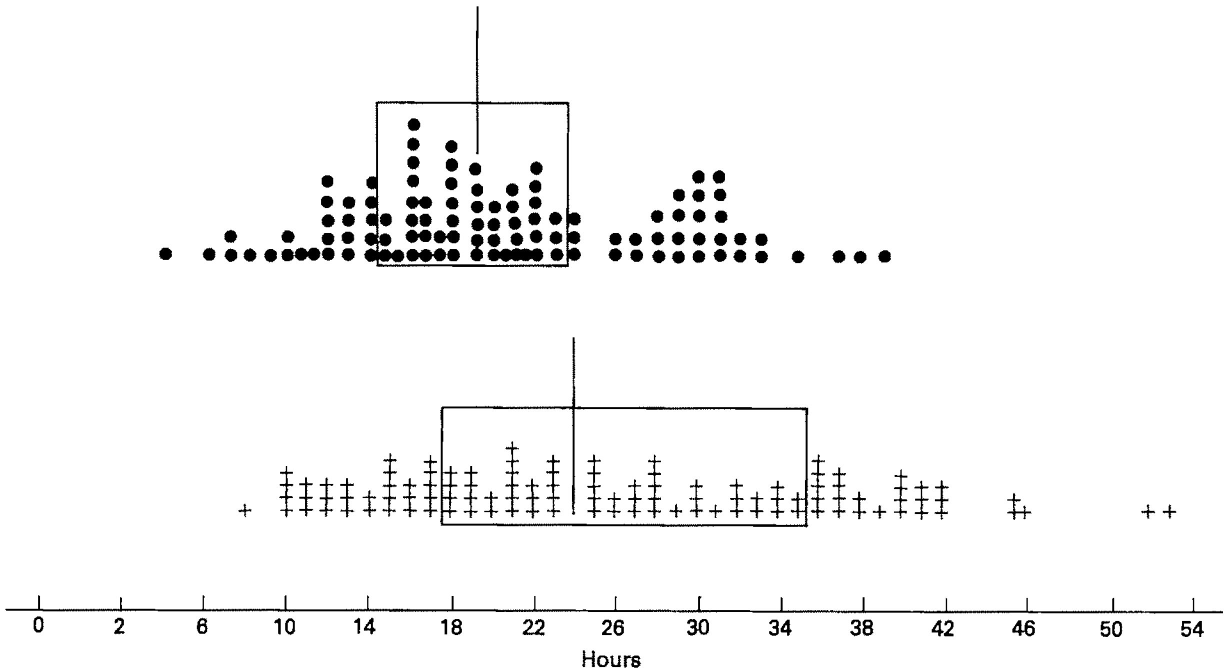


Fig. 2. The distribution of prelabour rupture of membranes to delivery interval (h) in the two management groups; (+) conservative management (●) active managements with PGE$_2$ gel. The vertical lines represent the median and the boxed area the 95% CI for each group.

32 (29%) women managed conservatively compared with 3 (3%) in the PGE$_2$ treated group (95% CI 14–40%, $P<0\cdot001$). In the conservative group 56 (51%) required oxytocin augmentation compared with 34 (31%) in the PGE$_2$ group ($P<0\cdot001$). Compared with conservative management, the use of prostaglandin was associated with significantly reduced intervals between PROM and the onset of uterine activity (two tailed t-test, 9·84, $P<0\cdot001$), between PROM and the initiation of oxytocin infusion (two tailed t, 8·00, $P<0\cdot001$), and between PROM and delivery ($Z = 3\cdot957$, $P<0\cdot001$, Fig. 2).

Mode of delivery

In the conservatively managed group 11% were delivered by caesarean section compared with 12% in the PGE group ($\chi^2 = 0\cdot780$, $P>0\cdot05$) (Table 5). Most caesarean sections were performed for failure to progress in labour. Two women in the PGE$_2$ group were delivered by caesarean section because an abnormal CTG developed within 4 h of PGE$_2$ insertion, both babies had good Apgar scores.

Table 5. Mode of delivery in the two study groups

	Conservative group (n = 110)	PGE$_2$ group (n = 110)
Vaginal delivery	98 (89%)	97 (88%)
Caesarean section (CS)	12 (11%)	13 (12%)
Indications for CS		
Prolonged first stage	9	8
Prolonged second stage	2	0
Fetal distress	1	4 *
Others	0	1
Total	12	13

*Two caesarean sections after the insertion of PGE$_2$ gel (see text).

Influence of cervical status

Of the women with a cervical score of ≤5, 49 of the 79 in the PGE$_2$ group (62%) were delivered within 24 h compared with 24 of the 69 (35%) in the conservatively managed group (35%) (difference 27%, 95% CI 12–42%) and they also had a significantly reduced requirement for oxytocin augmentation (difference 26%, 95% CI 10·5–41%) (Table 6). More than half of these women in the PGE$_2$ group required only one treatment with PGE$_2$ gel (2 mg) and the remaining 42% had a further 1 mg dose of PGE$_2$ gel 6 h later. There were no significant differences between the groups in mode of delivery. One woman in the PGE$_2$ group showed acute fetal distress on external CTG (4 h after the insertion of the second dose of gel). The cervix was unfavourable and she was delivered by emergency caesarean section.

Of the women with a favourable cervical score (≥6), most of those in the PGE$_2$ group were delivered within 24 h (difference 27%, 95% CI 8–45%), but there was no significant difference between the groups in requirement for oxytocin augmentation (difference 17%, 95% CI − 5 to 34%). Most of these women required only one dose of PGE$_2$ gel (2 mg). Again there was no significant difference in the mode of delivery between the two management groups. One woman in the PGE$_2$ group was delivered by caesarean section because of acute fetal distress 4 h after the insertion of the first dose of gel, the cervix was 4 cm dilated at caesarean section.

Perinatal data

Apgar scores at 1 and 5 min were comparable in the two

Table 6. Influence of cervical status and outcome of labour in the two study groups

	Cervical score ≤5		Cervical score ≥6	
Variable	Conservative group (n = 69)	PGE$_2$ group (n = 79)	Conservative group (n = 41)	PGE$_2$ group (n = 31)
PROM—delivery interval ≤24 h	24 (35%)	49 (62%)*	26 (63%)	28 (90%)**
Oxytocin augmentation	45 (65%)	31 (39%)*	11 (27%)	3 (10%)
Prostaglandin requirements				
2 mg	—	46 (58%)	—	25 (81%)
3 mg	—	33 (42%)	—	6 (19%)
Mode of delivery				
Vaginal	61 (88%)	70 (89%)	37 (90%)	27 (87%)
Caesarean section	8 (12%)	9 (11%)†	4 (10%)	4 (13%)†

Significance of difference between conservative and active management within cervical score category *P<0·01; **P<0·02.
†One CS in each group for acute fetal distress.
PROM = prelabour rupture of membranes.

management groups (Table 7). There were no significant differences in the duration of stay in the neonatal unit for observation. Three babies in the PGE$_2$ group and one in the conservative group were admitted with a diagnosis of mild hypoxia (95% CI, −9% to 13%). All were discharged within 72 h and no neonatal follow-up was required. Two babies (one in each group) were kept in the neonatal unit for up to 96 h on account of a prolonged PROM to delivery interval (95% CI, −20% to 23%). Eight babies (four in each group) were treated with parenteral antibiotics because of prolonged PROM to delivery interval. Of these, three babies in the conservative group and two in the PGE$_2$ group had a positive bacteriological screen. There were no neonatal deaths.

Table 7. Perinatal data in the two study groups

Variable	Conservative group (n = 110) n (%)	PGE$_2$ group (n = 110) n (%)
Apgar scores		
At 1-min		
<4	3 (3)	5 (5)
5–7	27 (25)	27 (25)
>8	80 (73)	78 (71)
At 5-min		
5–7	3 (3)	2 (2)
>8	107 (97)	108 (98)
Resuscitation required		
No resuscitation	92 (84)	91 (83)
Bag and mask	16 (15)	18 (16)
IPPV and intubation	1 (1)	1 (1)
Stay in SCBU		
Up to 24 h	3 (3)	1 (1)
25–48 h	3 (3)	2 (2)
>49 h	2 (2)	4 (4)
Indication for stay in SCBU		
Mild hypoxia	1 (1)	3 (3)
Low Apgar scores	5 (5)	4 (4)
Meconium inhalation	1 (1)	0 (4)
Jaundice	1 (1)	0

There were no significant differences between the two groups. SCBU = special care baby unit.

Discussion

The main concerns related to PROM are the occurrence of maternal and neonatal infection (Fayez *et al.* 1978; Johnson *et al* 1981; Daikoku *et al.* 1982). Infective morbidity significantly increases with a latent period of >24 h (Fayez *et al* 1978) and, therefore, a reduced interval between admission and delivery would be expected to reduce infective morbidity. Prostaglandins, because of their local priming effect (Calder *et al* 1977), should in theory be a useful adjunct agent for managing women with an unfavourable cervix. Our preference to use a newer preparation of prostaglandin (PGE$_2$ gel) was influenced by an earlier report (Mahmood 1989) in which PGE$_2$ gel (2 mg) was noted to be more effective than vaginal prostaglandin tablets (3 mg) for induction of labour in primigravidae with an unfavourable cervix and intact membranes.

Most women in the PGE$_2$ treated group started to labour and had a significantly reduced requirement for oxytocin augmentation, most of them were delivered within 24 h of PROM, compared with only 45% in the conservative group. This effect appears to be more marked in women with a favourable cervical score. However, a closer analysis of the data shows that the PROM to delivery interval was not exactly halved in the PGE$_2$ group compared to those managed conservatively. Although the observed reduction in the PROM—delivery interval in the PGE$_2$ group was statistically significant, the mean reduction was only 7 h. It can be argued that this reduction may be related to an earlier start of oxytocin augmentation in the PGE treated group. The caesarean section rate was the same in both study groups, as was the occurrence of infection. While accepting that our modified plan of active management with PGE$_2$ did significantly reduce the PROM to delivery interval, our caesarean section rate of 11% was still higher than the 7% reported by Macaulay *et al.* (1989). In this context, it must be noted that two women in the PGE$_2$ group required caesarean sections on account of uterine hyperstimulation and subsequent development of fetal distress. We suspect that this may be related to uncontrolled prostaglandin absorption, either into the amniotic cavity or into the maternal circulation. At least one caesarean section in the woman with a favourable cervix was potentially avoidable and these women need to be treated cautiously, the use of β-sympathomimetic agonists should have been considered. More work is required to study the effect of lower dosage of PG gel especially in women with favourable cervices.

The risk of clinically significant neonatal infection is 2–5% (Fayez *et al.* 1978; Duff *et al.* 1984). Our study did not report any significant differences in neonatal infective morbidity but our sample size was not sufficient to differentiate between our treatments on these outcomes. Only multicentre clinical trials will be able to prove whether active management with PG can significantly reduce the risk of neonatal infection in preference to conservative management. To demonstrate a 50% reduction (α 0·05, β 0·20; power 0·80) 2000 women would be required in each study arm.

However, we also acknowledge the virtues of the conservative approach in the management of these patients especially in units with a chronic shortage of midwifery staff. The practical implication is that spontaneously labouring women are easier to manage than those actively managed with intravenous oxytocin which requires the constant presence of trained nursing staff and increased need for fetal monitoring. The results of this study suggest that more work is still needed, especially in the management of those women where uterine activity fails to establish 24 h after the SROM. Since neither approach to management offered any particular advantage over the other in terms of caesarean section rate or neonatal infectious morbidity, perhaps the patients should be given the choice.

Acknowledgments

We thank the midwives and the medical staff in the labour ward and neonatal unit for their cooperation and Evelyn Laing for secretarial services.

References

Calder A. A., Embrey M. P. & Hillier K. (1974) Extra-amniotic prostaglandin E_2 for the induction of labour at term. *J Obstet Gynaecol Br Commonw* **81,** 39-46.

Conway D. I., Prendiville W. J., Morris A., Speller D. C. E., Stirrat G. M. (1984) Management of spontaneous rupture of the membranes in the absence of labor in primigravid women at term. *Am J Obstet Gynecol* **150,** 947-951.

Daikoku N. H., Kaltreider F., Khouzami V. A., Spence M., Johnson J. W. C (1982) Premature rupture of membranes and spontaneous preterm labour: maternal endometritis risks. *Obstet Gynecol* **59,** 13-20

Duff P., Huff R. W. & Gibbs R. S. (1984) Management of premature rupture of membranes and unfavourable cervix in term pregnancy. *Obstet Gynecol* **63,** 697-702.

Ekman-Ordeberg G , Uldbjerg N. & Ulmsten U. (1985) Comparison of intravenous oxytocin and vaginal prostaglandin E_2 gel in women with unripe cervices and premature rupture of membranes. *Obstet Gynecol* **66,** 307-310

Fayez J A., Hasan A. A., Jonas H. S. & Miller G. L. (1978) Management of premature rupture of the membranes. *Obstet Gynecol* **52,** 17-21.

Hauth J. C., Cunningham F. G. & Whalley P. J. (1977) Early labour initiation with oral PG E_2 after premature rupture of the membranes at term. *Obstet Gynecol* **49,** 523-526.

Johnson J. W. C , Daikoku N. H., Niebyl J. R., Johnson T. R. B., Khouzami V. A. & Witter R. F. (1981) Premature rupture of the membranes and prolonged latency. *Obstet Gynecol* **57,** 547-556.

Kappy K A., Cetrulo C. L., Knuppel R A., Ingardia C. J., Sbarra A. J., Scerbo J. C. & Mitchell G. W. (1979) Premature rupture of the membranes: a conservative approach. *Am J Obstet Gynecol* **134,** 655-661.

Kappy K. A., Cetrulo C. L., Knuppel R. A., Ingardia C. J., Sbarra A. J., Scerbo J. C. & Mitchell G. W. (1982) Premature rupture of the membranes at term: a comparison of induced and spontaneous labours. *J Reprod Med* **27,** 29-33.

Keirse M. J. N. C., Noort W. & Erwich J. J. H. M. (1987) The role of prostaglandins and prostaglandin synthesis in the pregnant uterus. In *Priming and Induction of Labour by Prostaglandins 'A State of the Art'* (Keirse M. J. N. C & de Koning Grans H. J., eds), Boerhaave Committee for postacademic medical education, Leiden, pp. 1-25.

Lange A. P., Secher N. J., Nielsen F. H. & Pederson G. T. (1981) Stimulation of labor in cases of premature rupture of the membranes at or near term. *Acta Obstet Gynecol Scand* **60,** 207-210.

Macaulay J., Turner M. J. & Gordon H. (1989) The use of vaginal prostaglandin E_2 tablets to induce labour in primiparae with an unfavourable cervix following spontaneous rupture of the membranes at or near term—a pilot study. *J Obstet Gynaecol* **9,** 193-195.

Magos A. L., Noble M. C. B., Wong T. Y. A. & Rodeck C. H. (1983) Controlled study comparing vaginal prostaglandin E_2 pessaries with intravenous oxytocin for the stimulation of labour after spontaneous rupture of the membranes *Br J Obstet Gynaecol* **90,** 726-731.

Mahmood T. A. (1989) A prospective comparative study on the use of prostaglandin E_2 gel (2 mg) and prostaglandin E_2 tablet (3 mg) for the induction of labour in primigravid women with unfavourable cervices. *Eur J Obstet Gynecol Reprod Biol* **33,** 169-175.

Morales W. J. & Lazar A. J. (1986) Expectant management of rupture of the membrane at term. *South Med J* **79,** 955-958

O'Driscoll J. K & Meagher D. (1980) Active management of labour. *Clin Obstet Gynaecol,* **Suppl 1,** W. B Saunders, London: pp. 27-28.

Rovinsky J. & Shapiro W (1968) Management of premature rupture of membranes I. Near term. *Obstet Gynecol* **32,** 855-866.

Schutte M. F., Treffers P. E., Kloosterman G. J. & Soepatmi S. (1983) Management of premature rupture of membranes: the risk of vaginal examination to the infant. *Am J Obstet Gynecol* **146,** 395-400.

Westergaard J G., Lange A. P., Pederson G. T. & Secher N. J. (1983) Use of oral oxytocins for stimulation of labour in cases of premature rupture of the membranes at term. *Acta Obstet Gynecol Scand* **62,** 111-116.

Yoder P R., Gibbs R. S., Blanco J. D., Castaneda Y. S. & St Clair P. J. (1983) A prospective, controlled study of maternal and perinatal outcome after intra-amniotic infection at term *Am J Obstet Gynecol* **145,** 695-701

Received 24 January 1991
Accepted 29 October 1991

British Journal of Obstetrics and Gynaecology
February 1992, Vol. 99, pp. 118–121

OBSTETRICS

Plasmodium falciparum malaria in pregnancy: a review

DILIP NATHWANI
Senior Registrar

PETER F. CURRIE
Registrar

J. GRAHAM DOUGLAS
Consultant

The Infection Unit, City Hospital, Aberdeen

STEPHEN T. GREEN
Senior Registrar

The Department of Infection and Tropical Medicine, Ruchill Hospital, Glasgow

NORMAN C. SMITH
Consultant

The Aberdeen Maternity Hospital, Aberdeen

The prevalence of *Plasmodium falciparum* malaria in the United Kingdom has risen steadily over the last decade with over 1000 cases reported in 1986 (Phillips-Howard *et al.* 1988). This has been attributed to the increased number of travellers to Africa exposed to the infection, and to greater risk of breakthrough as a result of the spread of chloroquine-resistant *P. falciparum* malaria (McGregor 1964). Although there has been no corresponding increase in deaths related to *P. falciparum* infection, the majority of deaths occurred in Britons who were likely to be non-immune. Non-immune pregnant women are particularly prone to falciparum malaria infection. Infection in the second or third trimester carries a bad prognosis (Warrell 1989). Complications include miscarriage, intrauterine death, preterm delivery and low birthweight (McGregor *et al.* 1983; Menon 1972). The principal maternal complications are severe hypoglycaemia, acute pulmonary oedema, anaemia, preterm labour and death (Warrell *et al.* 1990). In the recent recommendations for the prevention of malaria among travellers, women who are pregnant or likely to become so were advised to avoid travel to areas with chloroquine resistant *P. falciparum* because alternatives to chloroquine chemoprophylaxis, either mefloquine or doxycycline, are not currently licensed for chemoprophylaxis in pregnancy (CDC 1990).

We review the current management of *Plasmodium falciparum* malaria occurring in pregnancy as well as the problems of antimalarial chemoprophylaxis.

Correspondence: Dr Dilip Nathwani, Senior Registrar, The Infection Unit, City Hospital, Aberdeen AB9 8AU.

Clinical features of severe malaria in the non-immune pregnant women

Most patients with falciparum malaria present to their doctors with minimal or nondescript symptoms. This results in the common misdiagnosis of influenza in patients who die a few days thereafter. Feverishness and headache and slight scleral icterus are the most frequent symptoms and signs, respectively. Any other symptoms at presentation are likely to be those of complications, with confusion the most important, because it is the earliest sign of cerebral malaria (Ellis 1989). Pregnancy enhances the clinical severity of *P falciparum* malaria. In pregnant women with little or no previous experience of the disease, *P. falciparum* causes severe clinical illness (hypoglycaemia, anaemia and acute pulmonary oedema are common complications), substantial maternal mortality, increased rates of miscarriage and preterm labour, stillbirth and low birth weight offspring. These consequences seem unmodified by maternal parity in non-immune women but in semi-immune pregnant women living in endemic areas parity appears to influence susceptibility to an important degree. In this group primiparous women are at increased risk of complications (McGregor 1987; Paluka *et al.* 1988).

The increased propensity to severe malaria in pregnancy may be explained by immune depression related either to high levels of total cortisol (Vleugels *et al.* 1987) and/or decreased cellular immunity (especially in the third trimester) (Sholapurkar *et al.* 1990). The adverse consequences for the fetus may be the result of preferential parasite sequestration to the placenta (Galbraith *et al.* 1980). Occasionally, particularly in non-immune women, malarial parasites can cross the placental barrier and enter the fetal circulation giving rise to congenital malaria (Strang *et al.* 1984). The fetus is, however, relatively well protected from malaria by maternal antibodies and fetal haemoglobin is largely resistant to the malaria parasite (Pasval *et al.* 1976).

Management of *P. falciparum* malaria and its complications in pregnancy

Severe malaria in pregnancy is a medical emergency and the patient should be managed in an intensive care unit if possible. A multidisciplinary team approach to management based around an obstetrician and infectious disease physician is important. The principles of managing severe falciparum malaria in pregnancy involve early intravenous antimalarial chemotherapy, the detection and management of the complications of falciparum infection and monitoring fetal well-being.

Before drug therapy is started, a rapid clinical as well as laboratory assessment of the patient should be made. The level of hydration must be monitored as orthostatic hypotension may be exaggerated by antimalarial drugs. Hypovolaemia should be corrected with an appropriate plasma expander such as plasma protein solution or Haemacel. If consciousness is impaired, the blood glucose must be checked rapidly and if this is not possible a test dose of intravenous glucose should be given to exclude hypoglycaemia. Temperature should be measured rectally and temperatures above 39·5C° may cause confusion, coma and permanent brain damage. Such patients should be cooled by removing their clothes, the use of a fan, tepid sponging and paracetamol. Hypoglycaemia and hyperpyrexia may lead to fetal distress but are rapidly correctable. Important laboratory investigations include the parasite count, haematocrit, platelet and white cell counts, serum electrolytes, urea and creatinine, blood glucose, blood culture and arterial blood gas tensions, pH, bicarbonate and lactate.

Drug treatment in pregnancy

In severe and complicated malaria, antimalarial drugs should be started as soon as possible: delay may prove fatal. Where infection has been acquired in a chloroquine resistant zone, and if it has broken through prophylaxis or when the geographical origin or species is uncertain, quinine is the treatment of choice (Phillips 1988). The altered pharmacokinetic profile of quinine in pregnancy is not of sufficient magnitude to warrant changes in dose recommendations compared with nonpregnant adults. Ideally the drug should be given by a controlled rate intravenous infusion until the patient is able to swallow. A loading dose of quinine (20 mg salt/kg over 4 h) is required to achieve therapeutic concentrations as quickly as possible (the loading dose should not be given if quinine or mefloquine was taken 12–24 h earlier). Subsequent maintenance doses are 10 mg salt/kg as 4 h infusions every 8 h. Once the patient can swallow, equivalent oral doses are given for 7 days. Initial dosing, dependent on the volume of distribution, should not be reduced if there is renal impairment. Only the maintenance dose need be reduced in renal failure. With chloroquine sensitive falciparum infection, a slow intravenous infusion of chloroquine may be more rapidly effective and has fewer toxic effects than quinine.

Although quinine in pregnancy is oxytocic (Onnis & Grella 1984) its use in pregnant women is considered to be essential and a recent study in 30 women who were more than 30 weeks pregnant did not detect any uterine stimulation or fetal distress associated with the use of intravenous quinine (Looareesuwan *et al.* 1985). The major adverse effect is hypoglycaemia (White *et al.* 1983). This is discussed below. Although quinine is excreted in breast milk the total amount of drug consumed by the infant is unlikely to be clinically significant (Phillips *et al.* 1986).

Mefloquine, a quinolone methanol, appears to be safe and effective in the treatment of falciparum malaria in pregnancy (Collingnon *et al.* 1989). In treating uncomplicated falciparum malaria in nonpregnant patients it was found to clear parasitaemia more effectively than quinine, did not cause hypoglycaemia and also caused less tinnitus (Phillips *et al.* 1986). Pyrimethamine-containing drugs may sometimes be used in certain areas in combination with sulphonamides for treating *P falciparum* malaria sensitive to these drugs (e.g., in some areas of Africa and the Indian subcontinent). Severe falciparum malaria with a high parasitaemia in pregnancy has been treated successfully with exchange transfusion (Malin *et al.* 1990). The place of this form of therapy, however, remains unclear.

When appropriate parenteral antimalarials are unavailable, alternative measures must be considered as the consequences of delay are grave. Chloroquine might be life saving if resistance is mild. Chloroquine or quinine may be given via a nasogastric tube in an unconscious patient.

Complications

Hypoglycaemia

This is very common in pregnant women with severe falciparum malaria and treatment with quinine will exacerbate this. Quinine-induced islet cell stimulation leading to hyperinsulinaemia is the most common cause of hypoglycaemia (White *et al.* 1983) but increased glucose consumption and impaired gluconeogenesis are other mechanisms (Warrell, Molyneux & Beales 1990).

Hypoglycaemia may be prevented by administering continuous intravenous 5–10% dextrose when quinine is being given. Abnormal behaviour, sweating or sudden loss of consciousness, particularly in a patient receiving quinine, should be considered to be hypoglycaemia until proven otherwise. The BM Stix can provide rapid diagnosis and blood glucose should be checked and 10% dextrose should be infused intravenously. If the diagnosis is in doubt a therapeutic test of 25–50 ml of intravenous 50% dextrose should be tried. In a minority of patients where recurrent hypoglycaemia is a problem, glucose solution through a nasogastric tube is preferable to repeated infusions of intravenous hypertonic 50% glucose which may lead to circulatory overload, rebound hyperinsulinaemia, hypokalaemia and acidosis.

Acute pulmonary oedema

Pregnant women with *P. falciparum* malaria are particularly prone to developing acute pulmonary oedema (Fein *et al.* 1978). In pregnancy maternal blood volume increases, the changes in plasma volume being proportionally greater than the increase in red cell mass. Although this increased fluid load is believed to be an important risk factor for developing pulmonary oedema (Weatherall & Abdalla 1982) a number of patients also develop this complication despite normal or negative fluid balance (Lawson 1967). Hyperparasitaemia and renal failure are important predisposing factors. Pulmonary oedema may be present on admission or develop suddenly several days later. An increase in the respiratory rate or dyspnoea often precedes other chest signs and are an important early indicator of this complication. Fluid overload during labour makes women particularly susceptible to pulmonary oedema. This may occur before delivery or immediately after delivery with the sudden increase in peripheral vascular resistance that accompanies separation of the placenta. If pulmonary oedema develops, the patient should be propped upright, given high concentration of oxygen by any convenient method followed by intravenous frusemide. To prevent this potentially fatal complication, fluid replacement must be strictly controlled. This may be achieved by maintaining the central venous pressure between zero and 5 cm water and nursing the patient propped up at an angle of 45°.

Anaemia

In non-immune pregnant women *P. falciparum* malaria will inevitably produce anaemia. The mechanisms are multifactorial and complex and include haemolysis, hyperferritinaemia, bone marrow dyserythropoiesis and iron or folic acid deficiency (Weatherall & Abdalla 1982). Severe maternal anaemia is associated with perinatal mortality, maternal morbidity and increased danger of fatal post-partum haemorrhage (Warrell, *et al.* 1990). The haematocrit should be monitored and blood transfusion may be necessary if the haematocrit concentration falls below 20%. At this severity of anaemia there is also a high risk of acute right heart failure in labour (related to increased blood volume and peripheral vascular resistance after placental separation). In this situation patients should be transfused slowly with packed cells and given intravenous frusemide. An alternative is exchange transfusion which may be a safer method of correcting anaemia without precipitating pulmonary oedema.

Preterm labour

Falciparum malaria in non-immune subjects commonly induces uterine contractions which may lead to preterm labour. Their intensity and frequency are related to the level of the fever (Looareesuwan *et al.* 1985). Hyperthermia may cause preterm labour and fetal distress in women in late pregnancy and must be treated promptly (Warrell *et al.* 1990). Fetal distress is common although underdiagnosed. Preterm labour is associated with poor fetal prognosis in severe disease (Lawson 1967). Monitoring of uterine contractions and fetal heart rate is essential as this may detect asymptomatic uterine contractions, fetal tachycardia and late decelerations. Induction of labour or caesarean section may be necessary (Lawson 1967).

Bacterial infection

Other maternal complications which are less common include increased susceptibility to pneumococcal infection and Gram-negative septicaemia. The latter is usually derived from the gastrointestinal or urinary tract (following the use of an in-dwelling catheter). Blood cultures should be taken if bacterial sepsis is suspected, followed by best-guess broad spectrum intravenous bacteriocidal therapy (e.g., ceftazidime).

Antimalarial chemoprophylaxis

The risk of falciparum malaria in pregnancy far outweighs any harmful effects of chemoprophylaxis. However, none of the advocated regimens can guarantee complete protection. The importance of personal protective measures such as remaining in well-screened areas, use of mosquito nets when sleeping, wearing clothes that cover most of the body as well as using effective repellants (containing di-ethyl toluamide {DEET}) should be emphasised. Chloroquine is considered to be the drug of choice for malaria chemoprophylaxis in pregnancy and poses little teratogenic risk (CDC 1990). Proguanil has been used for several decades without any adverse efects. Mefloquine, doxycycline and primaquine are presently contraindicated for prophylaxis in pregnancy (CDC 1990) although Fansidar (pyrimethamine, sulfadoxine), mefloquine, halofrantine and quinine have been used in prophylaxis in pregnant Nigerian women (Fleming 1990). Women who are pregnant or planning to become pregnant should avoid travel to high risk areas with chloroquine resistant *P. falciparum* because antimalarial chemoprophylaxis is inadequate with the currently available drugs, although novel agents such as ginghaosu, mefloquine and riboflavin analogues are under investigation (Cook 1989).

References

Brooks M. H., Kiel F. W., Sheehy T. W. & Barry K. G. (1968) Acute pulmonary oedema in *falciparum* malaria. *N Engl J Med* **279**, 732-737.

Centers for Disease Control (CDC) (1990) Recommendations for the prevention of malaria among travellers. MMWR in *JAMA* **293**, 2729-2738.

Collingnon P., Hehir J & Mitchell D. (1989) Successful treatment of *falciparum* malaria in pregnancy with mefloquine. *Lancet* **i**, 967.

Cook G. C. (1989) The great malaria problem: where is the light at the end of the tunnel (editorial). *J Infect* **18**, 1-10

Ellis C. J. (1989) Malaria—clinical features in adults. *J Roy Soc Med* Suppl 17, **82**, 39-40

Fein L. A., Rackow E. C. & Shapiro L (1978) Acute pulmonary oedema in *Plasmodium falciparum* malaria. *Am Rev Resp Dis* **118**, 425-428.

Fleming A. F. (1990) Antimalarial prophylaxis in pregnant Nigerian women. *Lancet* **335**, 45.

Galbraith R. M., Fault W. P., Galbraith G. M. P., Holbrook T. W. & Bray R. S (1980) The human materno-foetal relationship in malaria. *Trans R Soc Trop Med Hyg* **74**, 52-72.

Lawson J. B. (1967) Malaria in pregnancy. In *Obstetrics and Gynaecology in the Tropics* (Lawson J. B. & Steward D. B , eds), Edward Arnold, London. pp. 59-72.

Looareesuwan S., Phillips R. E., White N. J., *et al.* (1985) Quinine and severe *falciparum* malaria in late pregnancy. *Lancet* **ii**, 4-8.

Malin A. S., Cass P. L. & Hudson C. N. (1990) Exchange transfusion for severe *falciparum* malaria in pregnancy. *Br Med J* **300**, 1240-1241.

McGregor I. A. (1964) Studies in the acquisition of immunity to *Plasmodium falciparum* infection in Africa. *Trans R Soc Trop Med Hyg* **58**, 80-85.

McGregor I. A., Wilson M. E. & Billewicz W. Z (1983) Malaria infection of the placenta in The Gambia, West Africa; its incidence, relationship to stillbirth, birth weight, and placental weight. *Trans R Soc Trop Med Hyg* **ll**, 686-692.

McGregor I. A. (1987) Thoughts of malaria in pregnancy with consideration of some factors which influence remedial strategies. *Parassitologia* **29** (2-3), 153-163.

Menon R. (1972) Pregnancy and malaria. *Med J Malaysia* **237**, 115-119.

Onnis A. & Grella P. (1984) *The Biochemical Effects of Drugs in Pregnancy.* Ellis Horwood, Chichester, Vol. 2, pp. 426-432.

Paluka K. M., Moore M., Roy J., Ma-Disu M. (1988) Malaria infection in pregnant women in Zaire: the effects and potential intervention. *Ann Trop Med Parasitol* **82**, 113-120

Pasvol G., Weatherall D. J , Wilson P. S. M., Smith D. H. & Gilies H. M. (1976) Foetal haemoglobin and malaria *Lancet* **i**, 1269-1272.

Phillips R. E., Looareesuwan S., White N. J, Silamut K., Kietinun S. & Warrell D A (1986) Quinine pharmacokinetics and toxicity in pregnant and lactating women with *falciparum* malaria. *Br J Clin Pharmacol* **21**, 677-683.

Phillips R. E., Looareesuwan S., White N. J. *et al.* (1986) Hypoglycaemia and antimalarial drugs: quinidine and release of insulin. *Br Med J* **292**, 1319-1321.

Phillips R. E. (1988) Malaria treatment and prophylaxis. *Prescribers Journal* **28** (3), 72-77.

Phillips-Howard P. A., Bradley D J., Blaze M. & Hurn M. (1988) Malaria in Britain 1977-86. *Br Med J* **279**, 245-247.

Sholapurkar S. L., Mahajan R. C., Gupta A. N. & Wangoo A. (1990) Cellular immunity in pregnant and non-pregnant women with malaria infection. *Asia Oceania J Obstet Gynaecol* **16**, 27-32.

Strang A., Lachman E, Pitsoe S. B., Marszalek A. & Hugh Philpott R. (1984) Malaria in pregnancy with fatal complication. Case report. *Br J Obstet Gynaecol* **91**, 399-403.

Vleugels M P, Eling W. M., Rolland R. & De Graff R. (1987) Cortisol and loss of malaria immunity in human pregnancy. *Br J Obstet Gynaecol* **94**, 758-764.

Warrell D. A. (1989) Treatment of severe malaria. *J Roy Soc Med* Suppl 17, **82**, 44-51.

Warrell D. M., Molyneux M. E. & Beales P. F. (1990) Severe and complicated malaria. *Trans R Soc Trop Med Hyg* **84** (suppl 2), 1-65.

Weatherall D A. & Abdalla S (1982) The anaemia of *Plasmodium falciparum* malaria. *Br Med Bull* **38**, 147-151.

White N. J., Warrell D. A., Chanthavanich P. *et al.* (1983) Severe hypoglycaemia and hyperinsulinaemia in falciparum malaria. *N Engl J Med* **309**, 61-66.

British Journal of Obstetrics and Gynaecology
February 1992, Vol. 99, pp 122–125

FETAL AND NEONATAL MEDICINE

Antenatal testing to predict outcome in pregnancies with unexplained antepartum haemorrhage

R. A. AJAYI
P. W. SOOTHILL
S. CAMPBELL
K. H. NICOLAIDES

Fetal Surveillance Unit
Department of Obstetrics and Gynaecology
King's College Hospital
Denmark Hill
London SE5 9RS, UK

ABSTRACT

Objective To investigate whether Doppler studies of placental perfusion and antenatal tests for fetal hypoxia can identify reduced placental functional reserve in women with unexplained antepartum haemorrhage (APH).

Design A prospective, longitudinal study.

Setting Fetal Surveillance Unit, King's College Hospital, London.

Subjects 48 women with bleeding from the genital tract after 26 weeks gestation without a clinical diagnosis of abruption or ultrasound evidence of placenta praevia.

Interventions Fetal surveillance by Doppler measurements of the umbilical and uterine arteries, biophysical profile scoring and computerized measurement of the mean minute range of FHR variation.

Main outcome measures A poor outcome was defined by one or more of the following: (i) birthweight >2SD below the normal mean for gestational age and sex, (ii) abnormal FHR pattern in labour resulting in operative delivery, (iii) umbilical vein blood pH at delivery <7·15, (iv) a 5-min Apgar score <7.

Results Fifteen of the 48 pregnancies had a poor outcome; seven occurred in the 10 women delivered preterm (<37 weeks) and eight in the 36 women delivered between 37 and 42 weeks. Two women were delivered after 42 weeks and both infants had a good outcome. The results of Doppler studies of uterine and umbilical arteries, fetal biophysical profile or FHR variation were not significantly different between the two outcome groups. The 36 pregnancies delivered between 37 and 42 weeks were matched retrospectively for maternal age, parity and race with 36 pregnancies without APH; there was no significant difference in outcome between the women with unexplained APH and the matched comparison group.

Conclusion Morbidity related to unexplained APH is associated with preterm delivery rather than with damage to utero-placental function.

Unexplained antepartum haemorrhage (APH) occurs in about 5% of pregnancies and is associated with an increased perinatal morbidity and mortality rate (Chamberlain *et al.* 1978). It has been suggested that this perinatal damage results from either preterm labour (Willcocks 1971) or placental damage leading to reduced functional reserve (Scott 1981). The increased risk attached to these pregnancies has led many obstetricians to intervene by delivering such women when the fetus is mature (Scott 1981), adding to both fetus and mother the risks of induction of labour.

The aim of this study was to examine whether antenatal tests could help make obstetric intervention more selective. On the assumption that some cases of unexplained APH are due to small abruptions (Notelovitz *et al.* 1979) with consequent placental infarction, we hypothesized that Doppler studies of the utero-placental (uterine) or the feto-placental (umbilical) circulations would be abnormal (Morrow & Knox Ritchie 1988). Furthermore, fetal hypoxia resulting from placental damage could be detected by studies of fetal behaviour (biophysical profile) and fetal heart rate (FHR) pattern. To assess placental reserve we investigated fetal distress in labour and studied the birthweight of the infants as an indicator of long-term placental function.

Subjects and methods

Between June 1990 and January 1991 women with vaginal bleeding after 26 weeks gestation were referred to a fetal surveillance unit (FSU) (Soothill *et al.* 1991) which had approval from the local ethics committee. In 51 women the APH was unexplained because a clinical diagnosis of abruption was not made, ultrasound scanning excluded placenta praevia and a speculum examination did not reveal any local cause for the bleeding. Three patients were excluded from the analysis, one had twins and two with preterm prelabour rupture of membranes.

After the initial episode of bleeding, patients were admitted to hospital for 24–48 h and when the bleeding stopped, they were subsequently managed as an outpatient with 1–2 weekly visits to the FSU.

Correspondence: Dr P. W Soothill, Senior Lecturer/Consultant, Department of Obstetrics and Gynaecology, University College Hospital Medical School, 86–96 Chenies Mews, London WC1E 6HX.

Table 1. Criteria of poor outcome found in 15 patients with unexplained antepartum haemorrhage

	Criteria of poor outcome			
Subject no *	Operative delivery†	SGA	UV pH <7·15	5-min Apgar score <7
1	–	–	+	+
2	+	–	NA	–
3	+	–	+	–
4	+	–	+	+
5	+	+	NA	–
6	–	+	–	–
7	+	–	NA	–
8	+	+	+	–
9	+	–	–	–
10	+	–	+	–
11	+	–	NA	–
12	–	+	+	–
13	–	+	–	–
14	–	+	+	–
15	–	–	NA	+
No. positive	9	6	7	3

Abbreviations: SGA = small-for-gestational age (>2SD below the normal mean); UV = umbilical vein; NA = not available.

* Subject nos. 1–7 were delivered preterm (<37 weeks gestation).

† Abnormal fetal heart rate pattern in labour leading to operative delivery.

The following investigations were made: (1) Continuous wave Doppler studies (Doptek, Chichester, UK) of the uterine arteries (Campbell *et al.* 1983); the results were considered abnormal if on either side the blood velocity waveform had characteristic notches (Schulman *et al.* 1986) or the resistance index (RI) was >97·5th centile for gestational age (Aristidou *et al.* 1990). (2) Continuous wave Doppler studies of the umbilical artery (Trudinger 1988); this was considered abnormal if the pulsatility index (PI) was >97·5th centile. (3) The biophysical profile (Manning 1990), the score was considered abnormal if <8 or ≤8 in the presence of oligohydramnios (single deepest pool <2cm); the FHR component was considered abnormal if there were fewer than two accelerations in 20 min of recording. (4) Computerized analysis of the FHR pattern (Oxford 8000, Sonicaid Ltd., Chichester, UK) was used which averages the one-minute ranges of pulse intervals about the base-line (Dawes *et al.* 1985); a mean minute range <20ms was considered abnormal (Ribbert *et al.* 1991).

The criteria for poor outcome were at least one of the following: (1) birthweight >2SD below the normal mean for gestational age and sex (SGA) (Yudkin *et al.* 1987); (2) abnormal FHR pattern in labour resulting in operative delivery; (3) umbilical vein blood pH at delivery <7·15; and (4) 5-min Apgar score <7. Values for umbilical vein blood pH at delivery were available for only 27 of the 48 patients (56%), but otherwise the outcome data were complete.

We compared the outcome of pregnancies with unexplained APH with a matched comparison group using the same criteria. Matching for confounding variables (such as management of preterm labour, and elective delivery decisions) was not possible for women delivered outside 37–42 weeks. Therefore, the comparison group had to be restricted to term pregnancies. Thus, for each of the 36 women with APH who were delivered between 37 and 42 weeks the records of the next woman delivered on our labour ward who did not have bleeding after 26 weeks but who matched the study patient for maternal age (within 3 years), parity and race were reviewed.

Statistical analysis

Since in normal pregnancy uterine artery RI and umbilical artery PI change with gestation, individual values in this study were expressed as multiples of SD from the normal mean for gestation (delta score). The data were normally distributed and Student's unpaired *t*-test was used to compare the data from the good and poor outcome groups. Since there were large differences among women in the number of visits (2–7) to the FSU, comparisons between the two groups were made with the results from the following visits: (1) the first visit; (2) the last visit before delivery; and (3) the worst result of any visit.

Results

The mean gestational age at referral to the FSU following

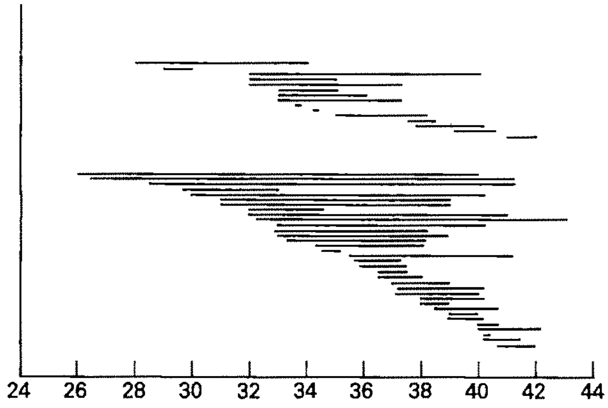


Fig. 1. The interval between presentation with unexplained antepartum haemorrhage and delivery. The 33 pregnancies with a good outcome are shown in the lower part of the figure and the 15 with a poor outcome are in the upper part.

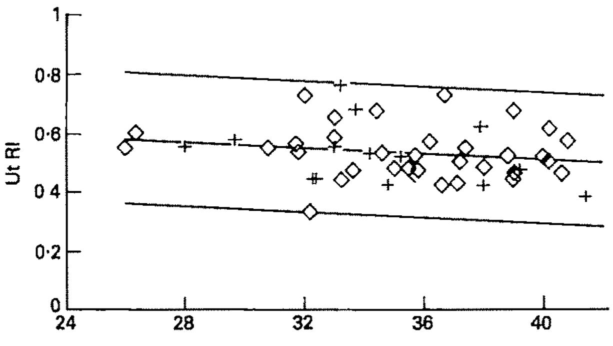


Fig. 2. The highest uterine artery resistance index (Ut RI) of any visit in 48 patients with unexplained antepartum haemorrhage compared to our normal range. + indicates a result from patients with a poor outcome and ◇ a result from patients with a good outcome.

Table 2. Results of tests for fetal well being at the first visit (1), last visit (2) and worst result of any visit (3) in 48 pregnancies with unexplained antepartum haemorrhage classified by outcome.*

			Significance		
Tests	Good outcome	Poor outcome	*t*	*P*	*n*
Uterine artery RI					
1	–0·09 (0·84)	–0·21 (1·0)	–0·45	0·66	48
2	–0·19 (0·67)	–0·30 (0·7)	–0·43	0·67	48
3	0·10 (0·81)	–0·10 (0·9)	–0·41	0·68	48
Umbilical artery PI					
1	–0·08 (0·87)	0·11 (1·3)	0·59	0·56	48
2	0·19 (0·99)	0·39 (0·9)	0·49	0·63	48
3	0·39 (0·93)	0·54 (0·8)	0·36	0·72	48
Fetal heart rate variation (ms)					
1	42·6 (11·3)	52·7 (17·3)	2·0	0·05	34
2	44·6 (9·6)	49·0 (15·4)	0·99	0·33	34
3	39·1 (10·1)	47·3 (16·8)	1·75	0·09	34

Results are mean (SD) values. The uterine artery RI (resistance index) and the umbilical artery PI (pulsatility index) are expressed as multiples of SD from the appropriate normal mean for gestation (delta score).

*All 48 pregnancies had a biophysical profile score of ≥8 at every investigation.

unexplained APH was 34·1 (range 26–40·6) weeks and the mean gestational age at delivery was 38·5 (range 30–43·1) weeks.

Review of the notes showed that none of the women was delivered because of the results of the tests carried out in the FSU and none of the babies died in the perinatal period.

A poor outcome occurred in 15 (31%) of the 48 pregnancies and some of the pregnancies fulfilled more than one of the criteria of poor outcome (Table 1). A retroplacental clot was observed at delivery on one occasion and this infant had a poor outcome. Although the mean gestational age at referral was not significantly different in the two outcome groups (poor, 34·15 weeks *vs* good, 34·13 weeks; $t = 0{\cdot}01, P = 0{\cdot}99$), the poor outcome group were born significantly earlier than the good outcome group (means: poor, 36·8 weeks *vs* good 39·3 weeks; $t = -3{\cdot}1, P = 0{\cdot}003$) (Fig. 1). Of the 10 women delivered <37 weeks (8 spontaneous and 2 elective for continuing haemorrhage) 7 had poor outcomes. In contrast only 8 of the 38 (22%) delivered >37 weeks had a poor outcome. The occurrence of poor outcome in the 36 women with unexplained APH who were delivered between 37 and 42 weeks was the same as that in the comparison group without APH (8 of 36).

There were no significant differences between the poor and the good outcome groups for the results of the first or last visits or the worst result of any visit (Table 2). The individual values of the highest uterine artery RI are shown in Fig. 2.

Discussion

The hypothesis that antenatal investigation of placental perfusion and fetal wellbeing would be able to identify those pregnancies in which unexplained APH is associated with placental damage and therefore fetal hypoxia was not substantiated. Indeed, the frequency of poor outcome in the pregnancies delivered at term was the same as that of controls, which suggests that unexplained APH does not reduce placental functional reserve. Since it appears that there was no placental damage in this group it is not surprising that the antenatal tests of placental function were normal.

The association between unexplained APH and perinatal morbidity could be explained if these haemorrhages are the result of small, clinically undetected, abruptions. Since abruptions can be predicted (Bewley *et al.* 1991) and detected (Morrow & Knox Ritchie 1988) by placental blood flow studies, the normal Doppler results in this study suggest that abruption was not the cause of the bleeding. Alternatively, the antenatal tests used may have been too insensitive to detect the changes we were looking for. Substantial changes in placental blood flow are probably required before they become detectable by continuous wave Doppler studies.

The greatest danger to these pregnancies was preterm delivery which occurred in 10 of the 48 women (21%) and seven of these fulfilled at least one of the criteria of poor outcome. However, even without APH, infants born after spontaneous preterm labour have a higher frequency of poor outcome, for example low Apgar scores (Goldenberg *et al.* 1984). Since we were unable to match these pregnancies with controls, we can not conclude that the high frequency of poor outcome in preterm pregnancies with unexplained APH was because of the APH alone. Indeed, the antenatal tests did not predict outcome even in this group so we have no evidence of placental damage. In a previous retrospective study of 307 women with unexplained APH, without the advantage of the antenatal tests of placental function, Willcocks (1971) concluded that 'the fetal risk in these cases is related to prematurity' and 'there is usually no need to terminate the pregnancy and spontaneous labour can be awaited'.

The results of the present study suggest that chronic fetal hypoxia is not a common feature in pregnancies complicated by unexplained APH and therefore there is a limited role for fetal surveillance or prophylactic elective delivery in the fetal interest.

Acknowledgments

We would like to thank Sister Jane Gibbs. R.A.A. was supported by a grant from the South East Thames Regional Health Authority (Lors grant 90/11).

References

Aristidou A., Van den Hof M. C., Campbell S. & Nicolaides K. H. (1990) Uterine artery Doppler in the investigation of pregnancies with raised maternal serum alpha-fetoprotein. *Br J Obstet Gynaecol* **97,** 431-435.

Bewley S., Cooper D. & Campbell S. (1991) Doppler investigation of utero-placental blood flow resistance in the second trimesters: A screening study for pre-eclampsia and intrauterine growth retardation *Brit J Obstet Gynaecol* **98,** 871-879.

Campbell S., Griffin D. R., Pearce J. M., Diaz-Recasens J. D., Cohen-Overbeek T., Wilson K. & Teague M. J. (1983) New Doppler technique for assessing utero-placental blood flow. *Lancet* **i,** 675-677.

Chamberlain G. V. P., Phillip E., Howlett B. & Masters K (1978) *British Births, 1970 Volume 2 Obstetric Care,* Heinemann. Medical Books, London, pp. 54-79.

Dawes G. S., Redman C. W. G. & Smith J. H. (1985) Improvements in the registration and analysis of fetal heart rate records at the bedside. *Br J Obstet Gynaecol* **92,** 317-325.

Goldenberg R. L., Huddleston J. F. & Nelson K. G. (1984) Apgar scores and umbilical artery pH in preterm newborn infants *Am J Obstet Gynecol* **149,** 651-654.

Manning F. A. (1990) The fetal biophysical profile score: current status. *Obst Gynecol Clin North Am* **17,** 147-162.

Morrow R. J. & Knox Ritchie J. W. (1988) Uteroplacental and umbilical artery blood velocity waveforms in placental abruption assessed by Doppler ultrasound. Case report. *Br J Obstet Gynaecol* **95,** 723-724.

Notelovitz M., Bottoms S. F., Dase D F. & Leichter P. J. (1979) Painless abruptio placentae. *Obstet Gynecol* **53,** 270-272.

Ribbert L. S. M., Snijders R. J. M., Nicolaides K H. & Visser G. H. A. (1991) Relation of fetal blood gases and data from computer-assisted analysis of fetal heart rate patterns in small for gestation fetuses *Br J Obstet Gynaecol* **98,** 820-823.

Schulman H., Fleischer A., Farmakides G., Bracero L., Rochelson B. & Grunfield L. (1986) The development of uterine artery compliance as detected by Doppler ultrasound. *Am J Obstet Gynecol* **155,** 1031-1036.

Scott J. S. (1981) Antepartum haemorrhage. In *Integrated Obstetrics and Gynaecology for Postgraduates,* 3rd edn (Dewhurst J. ed.) Blackwell Scientific Publications, Oxford, p. 255.

Soothill P. W., Ajayi R., Campbell S., Gibbs J., Chandran R., Gibb D. & Nicolaides K. H (1991) Effect of a fetal surveillance unit on admission of antenatal patients to hospital. *Br Med J* **303,** 269-271.

Trudinger B. (1988) The umbilical circulation. *Seminars in Perinatology* **11:4,** 311-321.

Willcocks J. (1971) Antepartum haemorrhage of uncertain origin *J Obstet Gynaecol Br Commonw* **78,** 987-991.

Yudkin P. L., Aboualfa J. A., Eyre J. A., Redman C. W. G. & Wilkinson A. R. (1987) New birthweight and head circumference centiles for gestational ages 24–42 weeks. *Early Hum Dev* **15,** 45–52.

Received 16 May 1991
Accepted 16 September 1991

British Journal of Obstetrics and Gynaecology
February 1992, Vol. 99, pp. 126–127

FETAL AND NEONATAL MEDICINE

Second trimester amniocentesis in twin pregnancies: maternal haemoglobin as a dye marker to differentiate diamniotic twins

J. R. BEEKHUIS
H. W. A. DE BRUIJN
J. M. M. VAN LITH
A. MANTINGH

Department of Obstetrics and Gynaecology
University Hospital Groningen
Oostersingel 59, 9713 EZ Groningen
The Netherlands

ABSTRACT

Objective To review the use of a membrane-free haemolysate prepared from maternal blood to distinguish the amniotic sacs at amniocentesis in twin gestation.
Setting University Hospital, Groningen.
Method Haemoglobin solution prepared from maternal blood.
Subjects 63 twin pregnancies having amniocentesis.
Results The fetal loss before 28 weeks was 4%. There was no perinatal mortality. Dye was detected in the second sac in 9 of 24 women tested before 1985 and none of the 39 women since, no malformations could be ascribed to the use of the haemolysate.
Conclusion The use of the membrane-free haemolysate is safe, but the technique will probably gradually become redundant because of improved ultrasound.

Various methods are available to ensure that amniotic fluid is sampled from each amniotic sac during amniocentesis in twin pregnancies. Recently, intestinal obstruction was diagnosed in infants following the intra-amniotic injection of methylene blue in the second trimester of pregnancy (Nicolini & Monni 1990). Serious complications, such as haemolytic anaemia in adult patients who received methylene blue, were described many years ago (Evans & Keegan 1960) and neonatal haemolysis and hyperbilirubinaemia have been reported following intra-amniotic injection (Cowett *et al.* 1976; Spahr *et al.* 1980).

Other dye markers, such as indigo-carmine and congo red, have been used in early twin pregnancies and until now, no such harmful effects have been described (Jassani *et al.* 1980; Elias *et al.* 1980; Holbrook *et al.* 1987; Tabsh 1990; Bang *et al.* 1975; Palle *et al.* 1983; Bovicelli *et al.* 1983). Owing to the lack of information on the harmful properties of these dyes, we chose a membrane-free haemolysate, prepared from maternal blood, as a dye marker for amniocentesis; we have been using it since 1976. This report describes our experience with 68 twin pregnancies tested since then.

Subjects and methods

Women with a twin pregnancy came to the clinic 90 min before scheduled amniocentesis in the 16th week of gestation to have 10 ml of maternal blood taken.

The blood was heparinized and centrifuged for 10 min at 1200 *g*. The plasma and buffy-coat layer were discarded. Erythrocytes were washed twice with two volumes of 0·9% NaCl solution, centrifuged and suspended in 3 ml of sterile 0·9% NaCl solution. Erythrocytes were haemolysed by sonification for 15 s under cooling (a small probe was used, amplitude 20 μm, MSE, Loughborough, UK). Centrifugation for 20 min at 20 000 *g* and 5° C removed any cell debris. The supernatant was subsequently passed through a 0·8 μm and a 0·22 μm filter (Millipore, Molsheim, France) into a sterile syringe. The haemoglobin concentration should be sufficient to give an extinction of 0·35 at 575 nm after a 200-fold dilution. The preparation takes about 1 h.

The use of a longer-life solution of haematin which would not need to be woman-specific might avoid the preparation of a fresh haemolysate marker each time. However, such a haematin solution will not remain sufficiently stable when stored over a longer time (van Assendelft 1970). Moreover, old blood, occasionally found in amniotic fluid, is also haematin and colours amniotic fluid brownish. It would be, therefore, impossible to distinguish it from the haematin dye-marker.

The sites for the insertion of the needles were selected by ultrasound examination. After disinfection and local anaesthesia of the abdominal wall, an 18 gauge needle was inserted into one of the amniotic cavities. Approximately 20 ml of amniotic fluid was aspirated after which 2–4 ml of the haemoglobin solution was injected through the same needle into the first amniotic sac. In this way we could conclude that the first cavity had been re-entered at the second puncture if the amniotic fluid obtained had a clear orange-red colour. If blood-stained amniotic fluid was drawn, a small sample was centrifuged to check whether the supernatant was red-coloured.

From 1976 to 1990, we performed amniocentesis on 68 women with a twin gestation. In five of them we did not use the dye for various reasons, leaving a study group of 63 subjects.

Results

We used the haemoglobin preparation in 63 women during

Correspondence: J R. Beekhuis.

Table 1. Pregnancy outcome of twin gestations after second trimester amniocentesis using a maternal haemoglobin dye marker

Pregnancy outcome*	No. of infants
Born alive, no congenital malformations	118
Born alive, cheilognathopalatoschisis	1
Both fetuses died in utero	4
One fetus died in utero	1
Lost to follow-up	2
Total	126

*Information obtained at least one week after birth.

amniocentesis. In nine women, the dye was detected in the amniotic fluid sampled at the second amniocentesis: in eight of them directly after sampling and in one at the laboratory after centrifugation of the maternal erythrocytes. In two women, amniocentesis of the second sac was repeated but failed; in the remaining six, the difficult position of the second cavity made it very improbable that a second attempt would be successful. All these difficulties were encountered in the first 24 women who were tested before 1985. In the subsequent 39 women, amniocentesis of the second sac was possible and all the samples were clear. Analysis of the 117 samples of amniotic fluid showed no abnormal karyotype or raised α-fetoprotein level.

One woman was lost to follow-up. From the total group, 118 of the infants were born alive and without any known congenital malformation at the age of at least one week (Table 1). In one infant who had cheilognathopalatoschisis, we could reconstruct retrospectively that the dye had probably been injected into the amniotic cavity of the affected twin. One pregnancy ended in the intrauterine death of both fetuses one week after amniocentesis. Another pregnancy ended in intrauterine death 5 weeks after amniocentesis. This monochorionic pregnancy was complicated by polyhydramnios and *Escherichia coli* was cultured from one amniotic cavity after birth. In another case, intrauterine death of one twin had occurred at an unknown gestational age and we could not reconstruct whether this twin had been in contact with the dye. None of the stillborn children had congenital malformations.

Discussion

Intestinal obstruction associated with the use of methylene blue as a dye marker was diagnosed 9·5% of children born to mothers with twin pregnancies who underwent amniocentesis in the second trimester (Nicolini & Monni 1990). From 1976 till now, we have used a membrane-free haemolysate for amniocentesis in 63 twin pregnancies. Only one infant had cheilognathopalatoschisis, which is unlikely to be the result of amniocentesis in the 16th week, because the formation of the palatum and upper lip are completed before the 10th week of gestation (Langman 1981).

Intrauterine death of five fetuses occurred in three women before 28 weeks gestation, resulting in a fetal loss of 4%. In one case, this was probably the result of polyhydramnios, making the fetal loss due to amniocentesis 2·4%. The reported rates of miscarriage after mid-trimester amniocentesis in twin pregnancies differ greatly, but even 4% is not unusually high (Elias *et al.* 1980; Palle *et al.* 1983; Librach *et al.* 1984; Filkins *et al.* 1984; Pijpers *et al.* 1988). There was no perinatal mortality.

It is notable that all nine women in whom dye was detected in the second sample were tested before 1985. Since then, the improved quality of the ultrasound apparatus has made it almost always possible to identify the septum between the two gestational cavities. In conclusion, our results show that the membrane-free haemolysate dye marker derived from maternal erythrocytes, is a safe, non-harmful alternative if the position of the interamniotic membrane is not clear.

Acknowledgments

We would like to thank S. Friese, gynaecologist, for the idea of using maternal blood as a dye marker, B. T. H. M. de Wolf and R. W. de Vrij for their excellent technical assistance and R. Zwierstra, paediatric surgeon, for his help with the follow-up.

References

van Assendelft O. W. (1970) *Spectrophotometry of Haemoglobin Derivatives*, Van Gorcum & Comp., Assen, p. 72.

Bang J., Nielsen H. & Philip J. (1975) Prenatal karyotyping of twins by ultrasonically guided amniocentesis. *Am J Obstet Gynecol* **123,** 695-696

Bovicelli L., Michelacci L., Rizzo N. *et al* (1983) Genetic amniocentesis in twin pregnancy *Prenat Diagn* **3,** 101-106.

Cowett R. M., Hakanson D. O., Kocon R. W. & Oh W. (1976) Untoward neonatal effect of intraamniotic administration of methylene blue. *Obstet Gynecol* **48,** 74S-75S.

Elias S., Gerbie A B., Simpson J. L., Nadler H. L., Sabbagha R E. & Shkolnik A. (1980) Genetic amniocentesis in twin gestations. *Am J Obstet Gynecol* **138,** 169-174.

Evans J. P. & Keegan H. R. (1960) Danger in the use of intrathecal methylene blue. *JAMA* **174,** 856-859.

Filkins K., Russo J., Brown T., Schmerler S. & Searle B. (1984) Genetic amniocentesis in multiple gestations *Prenat Diagn* **4,** 223-226.

Holbrook R. H., Krovoza A. M., Schelley S. & Ferguson J. E. (1987) Biamnial elevated alpha-fetoprotein and positive acetylcholinesterase in twins, one with anencephaly. *Prenat Diagn* **7,** 653-655.

Jassani M N., Merkatz I. R., Brennan J. N. & Macintyre M. N. (1980) Twin pregnancy with discordancy for Down's syndrome. *Obstet Gynecol* **55,** 45S-46S.

Langman J. (1981) *Medical Embryology* 4th edn, Williams & Wilkins, Baltimore, London, pp. 282-294

Librach C. L., Doran T. A., Benzie R. J. & Jones J. M. (1984) Genetic amniocentesis in seventy twin pregnancies. *Am J Obstet Gynecol* **148,** 585-591.

Nicolini U. & Monni G (1990) Intestinal obstruction in babies exposed in utero to methylene blue. *Lancet* **336,** 1258-1259.

Palle C., Andersen J. W., Tabor A., Lauritsen J. G., Bang J. & Philip J. (1983) Increased risk of abortion after genetic amniocentesis in twin pregnancies. *Prenat Diagn* **3,** 83-89.

Pijpers L., Jahoda M. G. J., Vosters R. P. L., Niermeyer M. F. & Sachs E. S. (1988) Genetic amniocentesis in twin pregnancies. *Br J Obstet Gynaecol* **95,** 323-326.

Spahr R. C., Salsburey D. J., Krissberg A. & Prin W. (1980) Intra-amniotic injection of methylene blue leading to methemoglobinemia in one of twins. *Int J Gynaecol Obstet* **17,** 477-478.

Tabsh K. (1990) Genetic amniocentesis in multiple gestation: A new technique to diagnose monoamniotic twins. *Obstet Gynecol* **75,** 296-298.

Received 14 May 1991
Accepted 24 September 1991

British Journal of Obstetrics and Gynaecology
February 1992, Vol. 99, pp 128–131

FETAL AND NEONATAL MEDICINE

Association of moderate obesity with a poor pregnancy outcome in women with polycystic ovary syndrome treated with low dose gonadotrophin

DIANA HAMILTON-FAIRLEY
DEBORAH KIDDY
HAZEL WATSON
CATHERINE PATERSON
STEPHEN FRANKS

Department of Obstetrics and Gynaecology
St. Mary's Hospital Medical School
Norfolk Place
London W2 1PG, UK

ABSTRACT

Objective To assess the effect of moderate obesity on the outcome of induction of ovulation with low dose gonadotrophin in women with polycystic ovary syndrome (PCOS).

Design Retrospective analysis of women with PCOS treated consecutively. An analysis of the impact of obesity on outcome of pregnancy using data from the North West Thames Regional (NWTR) obstetric database was included for comparison.

Setting Induction of ovulation clinic at the Samaritan Hospital for Women (St. Mary's Hospital Group).

Subjects 100 women with clomiphene-resistant anovulation associated with PCOS. 75 were of normal weight (BMI 19–24.9 kg/m^2, lean group) and 25 were moderately overweight (BMI 25–27·9 kg/m^2, obese group).

Interventions Induction of ovulation using low doses of gonadotrophins with small, stepwise increments in dosage as required.

Main outcome measures Rates of ovulation, pregnancy and miscarriage; daily and total doses of gonadotrophin required for induction of ovulation.

Results The proportion of ovulatory cycles was significantly greater in the lean group (77%) compared with the obese group (57%) (χ^2 9·8, $P<0{\cdot}001$). Obese women required larger doses of gonadotrophin to achieve ovulation ($P<0{\cdot}001$). The proportion of women who achieved at least one pregnancy was similar in the two groups (39% *vs* 48%) but miscarriage was more frequent in the obese group (60% *vs* 27%; $P<0{\cdot}05$). This difference was independent of the baseline and/or mid-follicular luteinizing hormone (LH) concentration either before or during treatment. Analysis of data from the North West Thames Health Region obstetric database confirmed an increased risk of miscarriage in moderately obese women which was independent of maternal age.

Conclusions Moderate obesity in women with PCOS, treated with low dose gonadotrophin, is associated with an increased risk of miscarriage. This is reflected in the results of analysis of the effect of obesity on outcome of pregnancy in the general population. It is therefore important to encourage weight reduction in obese women with PCOS before considering therapy to induce ovulation.

Low-dose gonadotrophin therapy is a safe and effective method of inducing ovulation in women with clomiphene resistant polycystic ovary syndrome (PCOS). It is associated with a high proportion of uniovulatory cycles and, as a result, a low rate of multiple pregnancy (Polson *et al.* 1987; Sagle *et al.* 1991; Hamilton-Fairley *et al.* 1991). The cumulative conception rate, however, is lower than that reported for women with hypogonadotrophic hypogonadism treated with gonadotrophins and the prevalence of early pregnancy loss is greater (Dor *et al.* 1980). The reasons for this are not clear but raised baseline and/or mid-follicular serum luteinizing hormone (LH) have been associated with early pregnancy loss (Homburg *et al* 1988; Watson *et al* 1989; Regan *et al* 1990) and a poorer response to gonadotrophin therapy (Hamilton-Fairley *et al.* 1991). Raised LH levels are not, however, found in all poor responders or all pregnancy losses and it is therefore probable that other factors play a part.

Obesity occurs in 35% of patients with PCOS; obese women with PCOS are more likely to have menstrual irregularity and anovulation than lean women with PCOS (Kiddy *et al.* 1990; Conway *et al* 1989). In a recent study Kiddy *et al.* (1992) have shown that weight reduction improves menstrual pattern and, in the women presenting with anovulatory infertility, may restore ovulation and fertility. The aim of this study was to examine the effect of moderate obesity on the response of women with clomiphene resistant PCOS to low-dose gonadotrophin therapy. The association of reduced fertility and menstrual dis-

Correspondence: Dr D. Hamilton-Fairley.

turbance with obesity, and its improvement after weight loss, implied that a factor directly related to obesity and independent of the hypersecretion of LH associated with PCOS may be present. This led us to investigate the association between obesity and miscarriage in the general population by analysing data obtained from the North West Thames Health Region (NWTHR) obstetric database which are readily accessible to this department.

Subjects and methods

One hundred women with anovulatory PCOS who had not ovulated in response to clomiphene citrate, up to a maximum daily dose of 150 mg, were treated with low dose gonadotrophin; either human menopausal gonadotrophin (hMG-Pergonal) (83 subjects) or follicle stimulating hormone (FSH-Metrodin, both Serono, Welwyn Garden City, UK) (17 subjects) using the protocol we have described previously (Sagle *et al.* 1991). In that study, which was a randomized, controlled trial comparing FSH with hMG, we found no differences between the two treatments in endocrine outcome or in rates of ovulation, conception and miscarriage. The data obtained from the two treatments have therefore been pooled for the purpose of the present study.

The women presented with oligomenorrhoea ($n = 72$) or secondary amenorrhoea ($n = 28$). The mean duration of infertility was 4·2 years (range 2–14). Women with marked obesity. body mass index (BMI) >28 kg/m^2, tubal disease or who had partners with abnormal male function tests (total spermatozoa count $<40 \times 10^6$/ml or motility of <50% or both) were not included in this study. One woman who received donor insemination was included.

The diagnosis of PCOS was made primarily on ultrasound (Adams *et al.* 1986) but was associated with the finding of a raised serum LH and/or testosterone level. The mean LH level was 12·1 (SD 7) IU/L compared with a mean control value of 6·3 (SD 2·4) and the mean testosterone level was 3·0 (SD 1·4) nmol/l compared with 1·8 (SD 0·4) (Franks 1989).

Gonadotrophin was given by daily intramuscular injection and follicular growth was assessed primarily by ultrasound. Each cycle was started at a dose of one ampoule (75 IU) and this was continued for a minimum of 7 days (14 days in the first cycle) before increasing the dose by 0.5 ampoules (37·5 IU) if no follicle ≥12 mm was seen on ultrasound. The dose was increased in a stepwise fashion every 7 days if there was no ovarian response, to a maximum of three ampoules daily (225 IU). If a follicle of ≥12 mm was seen then the dose was maintained (maximum daily dose) until follicular maturation (diameter of ≥18 mm) was complete. Human chorionic gonadotrophin (hCG) 5000 U (hCG-Profasi, Serono UK) was given to induce ovulation and the serum progesterone level was measured 5–8 days later. Ovulation was confirmed if the progesterone level was ≥30 nmol/l when a single follicle was released and ≥40 nmol/l when two or three were released. hCG was withheld in the presence of more than three follicles ≥16 mm in diameter. Pregnancy was diagnosed by a serum β-hCG concentration of ≥25 IU/l and by the presence of an intrauterine gestation sac on ultrasound. Early pregnancy loss was defined as the failure of the fetus to develop beyond 8 weeks gestation estimated from the day of hCG administration.

The results of treatment were analysed after dividing the women into two groups; a lean group of 75 women with BMI of 19–24·9 and an obese group of 25 women with a BMI of 25–27·9. The indices studied were the proportion of ovulatory cycles, the maximum daily dose of gonadotrophin and total dose required to induce ovulation, the conception rate and outcome of pregnancy.

Statistical analysis

Statistical analysis of the proportion of ovulatory cycles, uni-ovulatory cycles and the frequency of miscarriage in the two groups used the χ^2 test with Yates' correction. Differences in the maximum daily (threshold) dose and in the total dose of gonadotrophin were analysed using the Mann–Whitney U test for unpaired data. The possible relation between miscarriage and moderate obesity was further studied by analysis of the NWTHR obstetric database (Maresh *et al.* 1986). The proportion of women in the NWTHR who had had one or more miscarriages before their first registrable birth was obtained. The relation between miscarriage, obesity and maternal age was modelled using logistic regression analysis. The results are presented as adjusted odds ratios.

Results

There was no difference in mean age between the lean and obese groups (29·8, SD 4·3 years *vs* 30·9, SD 3·7 years) nor in the duration of infertility. The proportion of women with secondary infertility was comparable; 16% in the lean group (12/75) and 20% in the obese group (5/25). The mean (SD) baseline LH and testosterone concentrations were similar in the lean and obese groups (LH: 10·2, SD 6·1 *vs* 13·1, SD 7.5 IU/l and testosterone: 2·97, SD 1·8 *vs* 2·99, SD 0·95 nmol/l) respectively.

The lean group received a total of 308 treatment cycles and the obese group 97 (Table 1). The proportion of ovulatory cycles was significantly higher in the lean group (77%) compared with 57% in the obese group (χ^2 9·8, $P<0{\cdot}001$) and the proportion of uniovulatory cycles was greater in the lean group (75% compared with 60%; χ^2 4·1, $P<0{\cdot}05$). The mean maximum daily (threshold) dose and total dose of gonadotrophin required to induce ovulation were significantly lower in the lean group than in the obese group (Mann–Whitney U test $z = 4{\cdot}9$ and 5·1 respectively, $P<0{\cdot}001$). The mean basal FSH level was similar in the two groups, lean group 4·6 (SD 1·9) and obese group 4·9 (SD 1·1) IU/l. The mean midfollicular FSH level (day 7 to 5 before hCG) was significantly greater in the obese group (6·1, SD 1·4 *vs* 5·4, SD 1·5 IU/l; $t = 3{\cdot}1$ $P<0{\cdot}001$), reflecting the higher doses of gonadotrophin required for induction of ovulation.

The conception rate was similar in the two groups; 29 of the 75 women (39%) in the lean group conceived 30 pregnancies compared with 12 of the 25 (48%) in the obese groups who conceived 15 pregnancies (Table 1). There were only two multiple pregnancies in this series, both in the lean group, one twin and one triplet pregnancy. The prevalence of early pregnancy loss was greater in the obese group (47%) compared with 27% in the lean group (χ^2 5·1 ($P<0{\cdot}05$). The type of gonadotrophin used (hMG or FSH) had no influence on the outcome

Table 1. Results of gonadotrophin therapy: Comparison between lean and obese women with polycystic ovary syndrome.

Variable	Lean group	Obese group	Significance of difference (*P*)
No. of women treated cycles	75	25	
Total number	308	97	
Ovulatory cycles	237 (77%)	55 (57%)	<0·01
Uniovulatory cycles	177 (75%)	33 (60%)	<0·05
Gonadotrophin dose			
Total no. of ampoules	14·9 (9·1)	28·4 (11)	<0·001
Maximum daily dose (IU)	85·1 (25·1)	125·9 (33·9)	<0·001
No. of women achieving a pregnancy	29 (39%)	12 (48%)	
No. of pregnancies established	30	15	
Miscarriages			
Total no.	8 (27%)	9 (60%)	<0·05
Early pregnancy loss	8 (27%)	7 (47%)	<0·05

Results are mean (SD) or *n* (%) values as appropriate.

of pregnancy. Of the five pregnancies which occurred after treatment with FSH, one was in an obese women (and resulted in early pregnancy loss) and four were in the lean group (2 miscarriages).

In the regional population the risk of miscarriage rose with an increasing BMI (Table 2). An association of maternal age with miscarriage has been reported (Alberman 1987) and was seen in our population. However, the increased risk of miscarriage in obese women remained the same after adjustment for maternal age, suggesting that obesity and maternal age have an independent association with miscarriage.

Discussion

This study confirms the efficacy and safety of low dose gonadotrophin therapy in women with anovulatory PCOS.

Obese women with PCOS are less likely to respond to clomiphene citrate than lean women (Polson *et al* 1989). They are therefore more likely to be referred for gonadotrophin therapy. Our policy was to exclude from treatment women with a BMI >28 although these results indicate that even moderately obese women with PCOS are poorer responders to gonadotrophin therapy than their lean counterparts. They are less likely to ovulate and, if they do respond, require a larger daily dose and total amount of gonadotrophin. The lower ovulation rate is not due to poor absorption since the mid-follicular levels of FSH were appropriately higher for the larger doses given in the obese group, so that obese women seem relatively resistant to the action of endogenous gonadotrophin.

Obesity does not seem to interfere with the chance of conception. The increased frequency of miscarriage is, however, significant and appears to be independent of raised LH concentrations since these were similar in the two groups. This is consistent with the findings of Kiddy *et al* (1990) who found no difference in the baseline LH levels between lean and obese women with PCOS. There must, therefore, be some other factor(s) in obese women which interferes with ovulation and reduces the chance of successful pregnancy. This possibility is strengthened by the finding, reported here, of an association of obesity with miscarriage, independent of age, in a large unselected population in which the majority of women conceived spontaneously.

In lean women with hyperandrogenism there is evidence of hyperinsulinaemia compared to weight-matched controls (Burghen *et al.* 1980; Dunaif *et al.* 1988; Conway *et al* 1990). This seems to be characterized by insulin resistance which is predominantly peripheral with little hepatic involvement (Peiris *et al* 1989). In obese hyperandrogenic women this peripheral insulin resistance is more marked (Robinson *et al* 1992) Kiddy *et al.* (1989, 1992) have shown that weight loss in obese women with PCOS causes a significant decrease in fasting serum insulin levels and an accompanying increase in sex hormone binding globulin (SHBG) concentrations. This leads to a reduction in circulating free testosterone levels although the total testosterone concentrations remain constant. There is now considerable evidence that insulin regulates (inhibits) hepatic secretion of sex hormone binding globulin both in vivo (Holly *et al* 1989: Weaver *et al.* 1990) and in-vitro (Plymate *et*

Table 2. The risk of one or more miscarriages before the first viable birth in 13 128 consecutive primiparous women in relation to maternal body mass index (BMI) and age.

Variable	*n*	Miscarriage	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)
BMI (kg/m^2)				
19–24·9	9239	1058 (11%)	—	—
25–27·9	2340	329 (14%)	1·27 (1·11–1·44)	1·26 (1·18–1·6)
≥28	1549	232 (15%)	1·36 (1·17–1·59)	1·37 (1·18–1·60)
Age (years)				
20–29	9917	1098	—	—
30–34	2450	366	1·41 (1·24–1·60)	1·42 (1·25–1·61)
>35	761	155	2·05 (1·70–2·48)	2·06 (1·70–2·49)

The adjusted odds ratios are presented in relation to reference categories of women with BMI 19–24·9 kg/m^2 and maternal age 20–29 years.

al. 1988; Singh *et al.* 1990). The precise mechanism of how, or whether, these insulin mediated changes in free testosterone affect ovulation is not yet fully understood. It is, therefore, possible to hypothesize that one of the factors affecting the response of obese women to gonadotrophin therapy and subsequent pregnancy outcome may be insulin resistance.

Our findings suggest that obesity, even when moderate, adversely affects the response of women with PCOS to low dose gonadotrophin therapy. The association of obesity with a poor pregnancy outcome is reinforced by a similar finding in the general population. Women who are overweight should therefore be advised to lose weight before conception in order to improve their chances of a successful outcome and, in the case of women with PCOS requiring gonadotrophin therapy, before considering treatment.

References

Adams J., Polson D. W. & Franks S (1986) Prevalence of polycystic ovaries in women with anovulation or idiopathic hirsutism. *Br Med J* **293,** 355-359.

Alberman E. (1987) Maternal age and spontaneous abortion in *Spontaneous and Recurrent Abortion* (Bennett M. J. & Edmonds D. K., eds), Blackwell Scientific Publications, Oxford, pp. 83-89.

Burghen G. A., Givens J. R., Kitabchi A. E. (1980) Correlation of hyperandrogenism with hyperinsulinism in polycystic ovarian disease. *J Clin Endocrinol Metab* **50,** 113-116.

Conway G. S., Honour J W. & Jacobs H. S. (1989) Heterogeneity of the polycystic ovary syndrome: clinical, endocrine and ultrasound features in 556 patients. *Clin Endocrinol* **30,** 459-470.

Conway G. S., Jacobs H. S., Holly J M. P. & Wass J. A. H. (1990) Effects of luteinising hormone, insulin, insulin-like growth factor-I and insulin-like growth factor small binding protein 1 in the polycystic ovary syndrome. *Clin Endocrinol* **33,** 593-603.

Dor J., Itzkovic D. G., Mashiach S, Lunenfeld B. & Serr D. M. (1980) Cumulative conception rate following gonadotrophin therapy. *Am J Obstet Gynecol* **136,** 102-105.

Dunaif A., Mandeli J., Fluhr H. & Dobrjansky A. (1988) Impact of obesity and chronic hyperinsulinaemia on gonadotrophin release and gonadal steroid secretion in the polycystic ovary syndrome *J Clin Endocrinol Metab* **66,** 131-139.

Franks S (1989) Polycystic ovary syndrome: a changing perspective. *Clin Endocrinol* **51,** 87-120

Hamilton-Fairley D., Kiddy D. S., Watson H., Sagle M. & Franks S. (1991) Low-dose gonadotrophin therapy for induction of ovulation in 100 women with polycystic ovary syndrome. *Human Reproduction* **6,** 1095–1099.

Holly J. M. P., Smith C. P., Dunger D. B. *et al* (1989) Relationship between the pubertal fall in sex hormone binding globulin and insulin-like growth factor binding protein. A synchronized approach to pubertal development? *Clin Endocrinol* **31,** 277-284

Homburg R., Armar N. A., Eshel A., Adams J. & Jacobs H. S. (1988) The influence of serum luteinizing hormone concentrations on ovulation, conception and early pregnancy loss in patients with polycystic ovary syndrome. *Br Med J* **297,** 1024-1028.

Kiddy D. S., Hamilton-Fairley D., Seppäla M, Koistenen R., James V. H. T. & Franks S. (1989) Diet induced changes in sex hormone binding globulin and free testosterone in women with normal or polycystic ovaries: correlation with insulin and insulin-like growth factor-1. *Clin Endocrinol* **31,** 757-763.

Kiddy D. S., Sharp P. S., White D. M., Scanlon M F., Mason H. D., Bray C. S., Polson D. W., Reed M. J. & Franks S. (1990) Differences in clinical and endocrine features between obese and non-obese subjects with polycystic ovary syndrome: an analysis of 263 consecutive cases. *Clin Endocrinol* **32,** 213-220.

Kiddy D S., Hamilton-Fairley D., Bush A., Short F., Anyaoku V., Reed M. J. & Franks S. (1992) Improvement in endocrine and ovarian function during dietary treatment of obese women with polycystic ovary syndrome *Clin Endocrinol* **36,** 105-111.

Maresh M., Dawson A. M. & Beard R. W (1986) Assessment of an online computerized perinatal data collection and information system. *Br J Obstet Gynaecol* **93,** 1239-1245.

Peiris A N, Aiman E. J., Drucker W D & Kissebah A. H. (1989) The relative contributions of hepatic and peripheral tissues to insulin resistance in hyperandrogenic women *J Clin Endocrinol Metab* **68,** 715–720

Plymate S., Matej L. A., Jones R. E. & Frioll K. E. (1988) Inhibition of sex hormone binding globulin production in the human hepatoma (Hep G2) cell line by insulin and prolactin. *J Clin Endocrinol Metab* **67,** 460-464.

Polson D. W., Mason H. D., Saldahna B Y & Franks S. (1987) Ovulation of a single dominant follicle during treatment with low dose pulsatile follicle stimulating hormone in women with polycystic ovary syndrome. *Clin Endocrinol* **26,** 205-212.

Polson D. W, Kiddy D. S., Mason H. D. & Franks S. (1989) Induction of ovulation with clomiphene citrate in women with polycystic ovary syndrome: the difference between responders and non-responders. *Fertil Steril* **51,** 30-34

Regan L., Owen E. J. & Jacobs H. S. (1990) Hypersecretion of LH, infertility and spontaneous abortion. *Lancet* **336,** 1141-1144.

Robinson S., Chan S.-P, Spacey S., Anyaoku V., Johnston D. G. & Franks S. (1992) Postprandial thermogenesis is reduced in polycystic ovary syndrome and is associated with increased insulin resistance. *Clin Endocrinol* (in press).

Sagle M. A., Hamilton-Fairley D, Kiddy D. S. & Franks S. (1991) A comparative randomized study of low dose human menopausal gonadotrophin and follicle stimulating hormone in women with polycystic ovary syndrome. *Fertil Steril* **55,** 46-50

Singh A., Hamilton-Fairley D, Koistenen R., Seppala M., James V. H. T. Franks S. & Reed M J. (1990) Effect of insulin-like growth factor type 1 (IGF-1) and insulin on the secretion of sex hormone binding globulin and insulin-like growth factor binding protein-1 (IBP-1) by human hepatoma cells. *J Endocrinol* **124,** R1-R3.

Watson H., Hamilton-Fairley D., Kiddy D. *et al* (1989) Abnormalities of follicular phase LH secretion in women with recurrent early miscarriage. *J Endocrinol* **123,** (Suppl) abstr 25.

Weaver J. U., Holly J. M. P., Kopelman P. G., Noonan K., Giadom C. G., White N., Virdee S. & Wass J. A. H. (1990) Decreased sex hormone binding globulin (SHBG) and insulin-like growth factor binding protein-1 (IGFBP-1) in extreme obesity *Clin Endocrinol* **33,** 415-422.

Received 3 May 1991
Accepted 20 October 1991

British Journal of Obstetrics and Gynaecology
February 1992, Vol. 99, pp. 132–134

FETAL AND NEONATAL MEDICINE

External ocular trauma in instrumental and normal deliveries

ROGER HOLDEN
DAVID G. MORSMAN
GERVASE M. B. DAVIDEK
GERARD M. O'CONNOR

Department of Ophthalmology

E. C. COLES

Department of Medical Statistics

ANDREW J. DAWSON

Department of Obstetrics & Gynaecology, University Hospital of Wales, Cardiff

ABSTRACT

Objective To compare the occurrence of external ocular trauma in instrumental and normal deliveries.

Design Prospective controlled study.

Setting University Hospital of Wales, Cardiff.

Subjects 133 babies born consecutively with the use of forceps and 133 control babies born without instrumentation to women matched for parity.

Interventions External ocular examination.

Main outcome measures The presence within 24 h of birth of corneal oedema, corneal abrasion, conjunctival chemosis, subconjunctival haemorrhage and lid oedema.

Results Lid oedema and multiple minor external ocular trauma occurred in 52 and 22 babies, respectively, in the instrumental delivery group and in 13 and 8 babies, respectively in the control group ($P<0.001$). Corneal abrasion occurred in two babies and corneal oedema in one baby after forceps delivery but in none of the control group. No more serious injuries occurred. All injuries resolved without long term sequelae.

Conclusion The frequency of sight threatening corneal trauma in instrumental deliveries is low. Specialist ophthalmic screening of these babies is not justified.

Since the turn of the century it has been recognized that one of the sequelae of forceps delivery is corneal trauma (Peters 1907; Reid 1930; Fewel 1933; Sugar & Airala 1971). This takes the form of vertical splits in Descemet's membrane which may result in transient corneal oedema leading to irregular astigmatism with resultant amblyopia and blindness in the affected eye (Angell *et al.* 1981). Methods of correcting the astigmatism with contact lenses and thus preventing the amblyopia have been described (Spencer *et al.* 1966; Hoffman *et al.* 1981). Ocular trauma also can occur following a normal delivery, the incidence being estimated between 12% and 40% (Gile 1960; Jain *et al.* 1980). Permanent sequelae from these injuries are rare. Less common but more dramatic injuries have been described (Duke-Elder 1972).

No recent study has been performed to assess whether clinically significant external ocular trauma, particularly corneal trauma, is more frequent after forceps than after normal deliveries in a modern obstetric unit. This prospective study was conducted by the Departments of Obstetrics and Ophthalmology at our teaching hospital.

Subjects and methods

Between October 1989 and March 1990, with appropriate ethical approval, two groups of babies were examined. Written consent for the examination was obtained from the mother. In one group an assisted vaginal delivery had taken place with either Anderson's, Kielland's or Wrigley's forceps. In the other group, there had been a normal vaginal delivery. At the time of the study vacuum assisted deliveries were not widely practised in this hospital. Babies of ≥37 completed weeks gestation, including multiple and breech births, were examined within 24 h of birth. Those admitted to the special care baby unit for reasons other than forceps trauma were excluded. Those in the assisted delivery group were examined consecutively, including those born out of working hours and at weekends. For each forceps delivery, a control was selected from women of the same parity who had been delivered normally within the same 24-h period of that forceps delivery (normal delivery group). The baby was examined in the mother's presence by an experienced ophthalmologist. A naked eye examination of the lids and anterior segments was performed, followed by a detailed examination of the corneae using a hand held magnifier with built in light source. The presence and degree of lid oedema, conjunctival chemosis, subconjunctival haemorrhage, corneal abrasion and corneal oedema were noted. Corneal abnormalities were recorded using the scheme described by Waring & Laibson (1977). After examination and recording of the findings, the duration of the second stage of labour was noted from the medical records. In the assisted delivery group, the type of forceps and details of procedures such as rotation were also noted.

Statistical analysis was by a comparison of two proportions

Correspondence: Roger Holden, Clinical Cataract Research Unit, Nuffield Laboratory of Ophthalmology, Walton Street, Oxford OX2 6AW

Table 1. Frequency of external ocular trauma in assisted delivery group and normal delivery group

	Forceps (n = 133) (%)	Normal (n = 133) (%)	P	CIDP (%)
Lid oedema	52 (31–47)	22 (10–23)	<0·001*	12 to 33
Subconjunctival haemorrhage	13 (5–16)	8 (3–12)	0·36†	–3 to 10
Conjunctival chemosis	5 (1–9)	0 (0–3)	0·06†	0 to 7
Corneal abrasion	2 (0–5)	0 (0–3)	0·5†	0 to 4
Corneal oedema	1 (0–4)	0 (0–3)	1·0†	0 to 2
Multiple	13 (5–16)	0 (0–3)	<0·001†	5 to 15

Results are proportions with 95% CI in brackets.
*Chi squared (Yates' correction)
†Fisher exact probability test.
CIDP = 95% CI for the difference between proportions.
Multiple = more than one of the five categories of external ocular trauma in one eye.

(χ^2 test) with Yates' continuity correction. Where the sample sizes were small Fisher's exact test was used. Confidence intervals for the population values and differences between proportions were calculated as described by Gardner & Altman (1989), using the associated software package.

Results

In the study period there were 1246 live births, 150 (12%) with the use of forceps. Of the 150 babies born by forceps, 133 (89%) were examined together with 133 controls. Of those not examined the reasons were: refusal by the mother, language difficulties and early discharge. Of the 133 mothers in each group, 106 were primiparae 19 had had one vaginal delivery before the index birth and eight had had more than one. There were two breech presentation in the forceps group. The one breech presentation in the control group was born by the Mauriceau-Smellie-Viet method. Five of the multiparous women in the assisted delivery group and one in the control group had had a previous caesarean section. The reasons given for the use of forceps were fetal distress in 57 (43%), prolonged second stage in 33 (25%), failure to progress in 27 (20%) and unrecorded in 16 (12%). Anderson's forceps were used in 97 (73%) of which 94 were classed as low outlet and three as mid cavity. Kielland's forceps were used in the 20 (15%) rotational deliveries and Wrigley's forceps were used in the remaining 16 (12%) forceps deliveries, all being classed as low outlet.

The occurrence of external ocular trauma in one or both eyes for each group is shown in Table 1. Lid oedema and multiple external ocular trauma were significantly more frequent in the assisted delivery group. The increased conjunctival chemosis is on the borderline of significance. There was one example of corneal oedema in the assisted delivery group, a rate of 0·75% (95% CI 0 to 4·2%). This involved a particularly difficult low outlet delivery with Anderson's forceps. There were several manifestations of external ocular trauma to one eye with a localized area of corneal oedema. There were also scalp and facial contusions. The corneal oedema resolved within 48 h. The child underwent a detailed ocular examination 9 months later. The visual acuities were normal without refractive or astigmatic error. Biomicroscopic examination of the corneae revealed no abnormalities.

Rotational forceps deliveries are potentially more traumatic than non-rotational deliveries. However, there was no significant difference in the occurrence of external ocular trauma between those born in this way and the remainder of the assisted delivery group (χ^2-test).

Discussion

Our study shows that minor ocular birth trauma is still more common with instrumental deliveries. Proposed causes for this include compression of the orbit during a prolonged labour (Hoffman *et al.* 1981) and inappropriate forceps design (Hibbard & McKenna 1990), though no cause has been proven. The technique of the attending obstetrician is also likely to be a factor. Minor ocular birth trauma, however, is not clinically important as these conditions resolve rapidly and completely without visual handicap.

Traumatic corneal oedema, on the other hand, poses a potential threat to vision (Angell *et al.* 1981). Previous reports have cited the use of forceps as a major factor in corneal birth trauma (Peters 1907; Reid 1930; Fewell 1933; Sugar & Airala 1971). The only previous systematic study of corneal oedema following forceps delivery found one case in 491 births; follow-up was not reported (Jain *et al.* 1980). To our knowledge there are no published reports on the frequency of ruptures in Descemet's membrane after instrumental deliveries.

With methods of treating the sequelae of corneal trauma being available (Hoffman *et al* 1981), the question arises as to whether specialist ophthalmic screening of babies born in this way is justified. In the present study, although the numbers examined are relatively small, corneal oedema was uncommon and the condition self limiting. We conclude that screening for what in our study was a benign and infrequent condition is not justified.

References

Angell L. K., Robb R. M. & Berson F. G. (1981) Visual prognosis in patients with ruptures in Descemet's membrane due to forceps injuries. *Arch Ophthalmol* **99**, 2137-2139.

Duke-Elder S. & Macfaul P. A. (1972) Injuries. Mechanical injuries. *System of Ophthalmology,* (Duke-Elder S., ed.), vol. 14, pt 1, Henry Kimpton, London, pp. 9-18.

Fewell A. G. (1933) Lesions of the cornea caused by birth trauma *Trans Am Ophthalmol Soc* **31**, 329-344.

Gardner M. J. & Altman D. G. (1989) *Statistics with Confidence. Confidence Intervals and Statistical Guidelines* British Medical Journal, London, pp · 28-33.

Gile C. L. (1960) Retinal hemorrhages in the newborn. *Am J Ophthalmol* **49**, 1005-1011.

Hibbard B. M. & McKenna D. M (1990) The obstetric forceps—are we using the appropriate tools? *Br J Obstet Gynaecol* **97**, 374-380

Hoffman R. F., Paul T. O. & Pentelei-Molnar J. (1981) The management of corneal birth trauma. *J Pediatr Opthalmol Strabismus* **18**, 45-48.

Jain I. S., Singh Y P., Gupta S. L. & Gupta A. (1980) Ocular hazards during birth. *J Pediatr Ophthalmol Strabismus* **17**, 14-16.

Peters A. (1907) An injury of the cornea caused by instrumental labour. *Ophthalmascope* **5**, 146-150.

Reid A. M. (1930) Birth injuries in Descemet's membrane *Trans Ophthal Soc U Kingdom* **50**, 615.

Spencer W. H., Ferguson W. J. Jnr , Shaffer R. N. *et al.* (1966) Late degenerative changes in the cornea following breaks in Descemet's membrane. *Trans Am Acad Ophthalmol Otolaryngol* **70**, 973-983.

Sugar H. S. & Airala M. A. (1971) Birth injuries of the cornea. *Arch Ophthalmol* **8**, 26-28.

Waring G. O., Laibson P. R. (1977) A systematic method of drawing corneal pathologic conditions. *Arch Ophthalmol* **95**, 1540-1542.

Received 19 March 1991
Accepted 11 September 1991

British Journal of Obstetrics and Gynaecology
February 1992, Vol. 99, pp. 135–140

FETAL AND NEONATAL MEDICINE

Doppler umbilical artery flow velocity waveforms in diabetic pregnancy

FRANK D. JOHNSTONE
Department of Obstetrics and Gynaecology
JUDITH M. STEEL
Department of Diabetic Medicine
NABIL G. HADDAD
Department of Obstetrics and Gynaecology
PETER R. HOSKINS
Department of Medical Physics
IAN A. GREER
Department of Obstetrics and Gynaecology
SARAH CHAMBERS
Department of Radiology

Simpson Memorial Maternity Pavilion and Edinburgh Royal Infirmary, Edinburgh, UK

ABSTRACT

Objective To assess the effect of uncomplicated diabetes on umbilical artery flow velocity waveforms (FVWs); to investigate the relation between glycaemic control and FVWs and the predictive value of umbilical artery FVWs for antenatal fetal compromise.

Design Prospective descriptive study.

Setting A large diabetic pregnancy clinic in a teaching hospital.

Subjects 128 pregnancies complicated by diabetes mellitus. 170 non diabetic women with no pre-existing or pregnancy complications.

Interventions In diabetic pregnancies, umbilical artery resistance index (RI) Doppler recordings and glycosylated haemoglobin were measured every 2 weeks from 28 weeks.

Main outcome measures Umbilical artery RI and antenatal fetal compromise defined as a non reactive, decelerative cardiotocograph and/or a biophysical profile score persistently <6 and leading to immediate caesarean section.

Results Uncomplicated diabetic pregnancies had FVW values similar to those in the non-diabetic range. Glycaemic control was unrelated to umbilical artery FVW values. Abnormal umbilical artery RI was found in nine pregnancies, these were more likely to show evidence of fetal compromise and to be associated with birthweights of <50th centile. In seven pregnancies there was evidence of fetal compromise, but only three of these pregnancies had abnormal FVW values.

Conclusions The non-diabetic range of umbilical artery RI values is appropriate for diabetic pregnancies. Long-term glycaemic control, within the range in this study, does not seem to affect umbilical artery RI. Abnormal umbilical artery RI is a significant predictor of fetal compromise in diabetic pregnancy, but fetal compromise can occur in association with normal RI values. Undue reliance should not be placed on normal FVW values in diabetic pregnancies.

The emerging role of Doppler flow velocity waveform (FVW) analysis in clinical practice is as a discriminator. FVWs will identify not only pregnancies at high risk of fetal compromise (Johnstone *et al.* 1988) but also those women with minimal risk who can be spared unnecessary intensive antepartum monitoring. For example we believe that in uncomplicated suspected intrauterine growth retardation intensive fetal monitoring is not necessary providing umbilical artery FVWs are normal and the clinical situation is stable (Haddad *et al.* 1988a). There is recent support for this view (Burke *et al.* 1990).

Whether this is also true in pregnancy complicated by diabetes mellitus is unclear. Previous reports include only small numbers of patients; 25 insulin dependent women among 43 diabetic pregnancies studied by Bracero *et al* (1987) and 35 by Landon *et al.* (1988). We studied umbilical artery FVWs in a larger number of women prospectively to investigate (i) the effect of uncomplicated diabetes, (ii) the relation with glycaemic control and (iii) the long term predictive value for antenatal fetal compromise.

Correspondence: Dr Frank D. Johnstone, Department of Obstetrics and Gynaecology, Centre for Reproductive Biology, 37 Chalmers Street, Edinburgh EH3 9EW, Scotland, UK

Subjects and methods

All diabetic women attending our clinic, and for whom Doppler was available, were invited to participate. For nearly 2 years, a randomized trial on use of Doppler restricted availability to half of all patients. Only diabetics receiving insulin have been included. Conservative criteria were used for initiating insulin treatment in gestational diabetics, that is, patients had an abnormal 75 g glucose tolerance test (usually plasma glucose >11·2 mmol/l at 2 h) and after treatment with diet still had pre-prandial glucose levels persistently >6·5 mmol/l. The White class (White 1965) and main pregnancy complications are shown in Table 1. 84% were established insulin dependent diabetics and 48% of these were White class D/F/R. Superimposed or *de novo* proteinuric pregnancy induced hypertension (PIH) was common (18%) and 30% had some hypertensive complications.

Table 1. White classification and main complications in 128 diabetic pregnancies

White classification	*n*
Discovered in pregnancy (all requiring insulin)	21
Established (insulin dependent before pregnancy)	
B	25
C	31
D	37
F/R	14
Total	128
Main complications	
Pre-existing hypertension	5
Non proteinuric gestational hypertension	9
Proteinuric gestational hypertension (including superimposed)	23
Auto-immune thyroiditis	5
Epilepsy	2
Sarcoidosis	2
Addison's disease	1
Recurrent pancreatitis	1
Myocardial infarction	1

Uncomplicated diabetic pregnancies were defined as those singleton pregnancies where the women were insulin dependent before pregnancy, were delivered at 36 weeks or later, did not have nephropathy or any hypertensive complications, did not have other significant pregnancy complications such as recurrent antepartum haemorrhage and did not have emergency caesarean section for antenatal fetal compromise or fetal distress in early labour.

Diabetic control was assessed by glycosylated haemoglobin concentrations, which were repeated approximately every 2 weeks throughout the third trimester. The normal non-diabetic range for our laboratory is 6–8%.

Fetal well-being was assessed in all pregnancies by biophysical profile scores (Manning *et al.* 1985) and cardiotocography (CTG) at least weekly, and usually twice weekly in late pregnancy. For the diagnosis of antenatal fetal compromise three criteria had to be fulfilled: (i) a non-reactive, decelerative cardiotocograph and/or a biophysical score persistently <6 (Manning *et al.* 1985); (ii) the patient was not in established labour; (iii) the diagnosis led to immediate emergency caesarean section.

Our normal reference series (Fig. 1) is based on an unpublished cross sectional study of 170 non-diabetic women. These women were recruited specially for this study, had no pre-existing or pregnancy complications, and gave birth to healthy babies weighing over the 10th centile (Forbes *et al.* 1982). The reference values are similar to the normal range established by others (Pearce *et al.* 1988). The values are slightly lower, but similar to those at 28, 34 and 38 weeks in the unselected population study by Beattie & Dornan (1989).

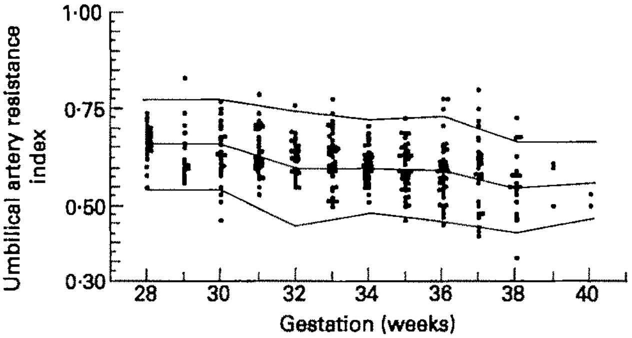


Fig. 1. Umbilical artery Doppler flow velocity waveform resistance index in uncomplicated diabetic pregnancy (lines indicate mean and 2SD for normal non diabetic pregnancy). Gestational ages were in completed weeks.

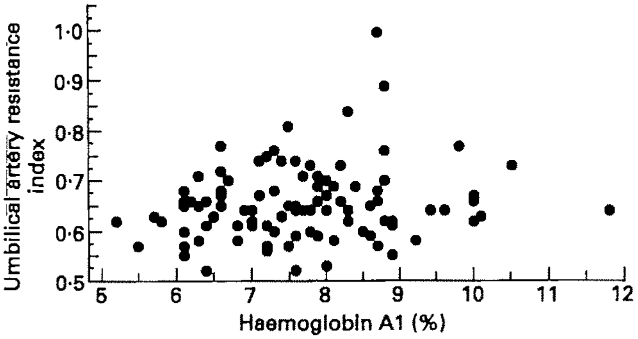


Fig. 2. Relation between umbilical artery resistance index at 30 weeks and mean glycosylated haemoglobin between 28–34 weeks.

Doppler studies

Doppler FVW recordings were obtained using a continuous wave Doppler with a 4 MHz transducer and spectrum analyser, filter level 60–80 Hz (Doptek, UK). For umbilical artery recordings, the operator adjusted the probe position until the characteristic waveforms were seen with a clearly defined outline and free from venous or other interference. Waveforms were only accepted if a clear continuous venous signal was visible in the reverse channel.

Usually routinely, and in all cases of difficulty, the operator located a loop of the umbilical cord with the assistance of a real time scanner. All signals were recorded on to an audio-cassette. For each recording the average resistance index (RI) of at least five umbilical artery FVWs was taken. The RI (calculated as the maximum systolic–end diastolic/maximum systolic) was used because it is simple, and other mathematical descriptions of the waveform have not improved prediction power (Hoskins *et al.* 1989a). Normalization of the index for heart rate has not been found to be helpful (Hoskins *et al.* 1989b) and no adjustment for heart rate was therefore carried out. Irregular traces due to fetal breathing were excluded (Hoskins *et al.* 1988).

The aim of this prospective study was to record serial umbilical FVWs from 28 weeks gestation, every 2 weeks. In prac-

Table 2. Relation between umbilical artery flow velocity waveform (FVW) and glycosylated haemoglobin

Gestation at FVW recording (weeks)	Gestational range of Hb A$_{1c}$	Number of pregnancies	Correlation coefficient	Probability
30	28–33	103	+0·17	0·09
	34–40	87	+0·09	0·42
36	28–33	106	+0·12	0·23
	34–40	99	+0·02	0·83

Table 3. All pregnancies with evidence of antenatal fetal compromise

Gestation at delivery (weeks)	Clinical	Monitoring data	Birthweight centile	Apgar score	Neonatal course	Last Doppler FVW	Number of abnormal Doppler FVWs
37	Proteinuric PIH	Non reactive CTG with decelerations	56	7/9	Normal	Abnormal	3/4
32	Very poorly controlled, massive polyhydramnios	BPP. 2/10 CTG: non reactive with decelerations	97	2/6	Ventilated for asphyxia then uneventful progress	Normal	0/1
37	Proteinuric PIH	At ARM for induction of labour, thick meconium staining. Fetal tachycardia and decelerations without any uterine activity	89	7/9	Normal	Normal	0/3
36	Poor control in early pregnancy	Fetal apnoea and prolonged non-reactive CTG, large late decelerations as soon as labour induced	25	4/7	Multiple cardiac anomalies NND	Normal	0/5
33	Very poorly controlled, previous IUD at 33 weeks	Decreased fetal movements, BPP apnoea and absent fetal movements. CTG long periods of non-react but occasional accelerations	82	7/9	UA pH 7·22	Abnormal	14/15
36	Uneventful pregnancy	Absent fetal movements for 6 h, BPP 2/10, CTG fixed tachycardia of 170 with reduced variability and no accelerations	99	8/9	Normal, UA pH 7·28	Normal	0/6
37	Hypertension, labetalol, aspirin	Persistently non-reactive CTG, absent fetal movements and fetal apnoea despite normoglycaemia	96	8/9	UV pH 7·15	Abnormal	4/8

Abbreviations: BPP, biophysical profile; CTG, cardiotocograph; IUD, intrauterine death; NND, neonatal death; CS, caesarean section; PIH, pregnancy induced hypertension, UA, umbilical artery, UV, umbilical vein, FVW, flow velocity waveform.

tice, the mean number of examinations per patient was 5·5 (SD 3·2).

When looking at large numbers of FVW recordings for each patient it is likely that several pregnancies would at some time have an abnormal result, therefore, the following definition of significant abnormality was used; at least 50% of recordings >mean + 2 SD for normal pregnancies, or else a single recording >mean + 4 SD. In practice all recordings abnormal by the second criterion were also abnormal by the first.

Statistics

Proportions were compared using the χ^2-test with Yates' correction, and associations were tested for significance by simple regression, with multiple regression analysis where appropriate. Results for uncomplicated diabetics were compared with our normal reference series by expressing their observations in terms of the number of SD (of normals) away from the mean of normals. These standardized observations were then tested against a hypothetical mean of zero, using a large sample Z test, to test whether the levels in uncomplicated diabetics differed from that of normals. Gestational age has been calculated in completed weeks.

Results

Of the 128 diabetic pregnancies studied there were 63 uncomplicated diabetic pregnancies as defined above. The results of the individual umbilical artery RI values in this group are shown in Fig. 1. Though there is a trend to higher values com-

Table 4. Nine pregnancies with significantly abnormal umbilical artery flow velocity waveform (FVW) values*

Umbilical artery FVW recordings								
Total number	Number >2SD	Any >4SD	White class	Gestation at delivery (weeks)	Birthweight centile	Antenatal fetal compromise	Mode of delivery	Clinical
4	3	No	C	37	56	Yes	ECS	Proteinuric PIH
7	7	Yes	F	32	45	No	ECS	Nephropathy, proliferative retinopathy, hypertension and superimposed PIH, myocardial infarction
3	3	Yes	F	38	46	No	Forceps	Nephropathy
2	2	Yes	B	36	14	No	ECS	Placenta praevia
6	3	No	B	39	46	No	SVD	Uneventful
15	14	Yes	C	33	82	Yes	ECS	Very poor diabetic control. Previous macrosomic stillbirth
14	8	No	R	38	25	No	CS (fetal distress in labour)	Myeloproliferative disorder polycythaemia
8	4	Yes	C	34	96	Yes	ECS	Hypertension, labetalol, aspirin
10	5	No	C	38	90	No	ECS	Recurrent bleeding throughout pregnancy, placenta praevia

* At least half of recordings were >mean + 2SD or any one recording >mean + 4SD for normal pregnancy.
ECS = emergency caesarean section; SVD, spontaneous vaginal delivery; PIH = pregnancy induced hypertension.

pared with normal non-diabetic pregnancies this is not statistically significant (standardized mean/SE = 1·74).

For the whole series, there was a weak, but statistically significant inverse association between the birthweight centile of the baby and the umbilical artery RI (at 30 weeks linear regression analysis showed $r = -0·21$, $n = 100$. $P = 0·04$ and at 36 weeks $r = -0·18$, $n = 109$, $P = 0·06$). On multiple regression analysis, with birthweight as the dependent variable including the variables maternal weight, smoking, hypertension, and duration of diabetes, the contribution of umbilical artery RI was no longer statistically significant ($P = 0·13$).

Mean glycosylated haemoglobin was not associated with umbilical artery RI (Table 2) and nor is there any suggestion of an association at any level of glycaemic control (Fig. 2).

Antenatal fetal compromise was diagnosed in seven pregnancies, their clinical details are shown in Table 3. All seven women were delivered immediately by emergency caesarean section. In only three pregnancies had the FVW been significantly abnormal as defined. The baby in the poorest condition, requiring ventilation for asphyxia, had normal umbilical artery FVW values earlier the same day. This patient had been transferred from another hosptial, and, because of non compliance, had had very poor diabetic control.

In nine pregnancies, shown in Table 4, umbilical artery FVW values were significantly abnormal (at least half the recordings >mean + 2 SD). Compared with the other diabetic pregnancies (Table 5) these were more likely to show evidence of fetal compromise ($P<0·01$) and to be associated with birth of babies weighing less than the 50th centile ($P<0·05$). One 21 year old patient, with nephropathy, retinopathy and hypertension, had absent end diastolic frequencies in the umbilical artery for 6 weeks. The pregnancy was complicated, with the patient having an acute myocardial infarction, but there was no obvious antenatal fetal compromise and the baby, when born at 32 weeks, was in good condition. Both mother and baby have done well.

Apart from this pregnancy, there was no serious maternal or neonatal morbidity. The only perinatal death in the series was a

Table 5. Comparison of clinical outcome between pregnancies with and without significantly abnormal umbilical artery flow velocity waveforms (FVW)

	Significantly abnormal FVW* ($n = 9$)	Other ($n = 119$)	Total diabetic pregnancies ($n = 128$)	Statistical significance	
				χ^2	P
Fetal compromise	3	4	7	9·32	<0·01
White class F/R	3	11	14	2·82	NS
PIH	3	20	23	0 63	NS
Birthweight <50th centile	5	21	26	5·27	<0·05

* At least half of recordings were >mean + 2SD or any one >mean + 4SD for normal pregnancy, PIH = pregnancy-induced hypertension.

baby with multiple cardiac anomalies, not diagnosed on ultrasound antenatally. The abnormalities were not considered surgically correctable and the baby died in the neonatal period.

Discussion

This study shows that in uncomplicated diabetic pregnancy, umbilical artery Doppler FVW values are not different from those found in non-diabetic pregnancies, confirming the report of Landon *et al.* (1989). The analysis of the standardized umbilical artery RI has the theoretical objection that the same woman may contribute more than once to the analysis. This does indeed increase the chance of a falsely significant result, but should not affect the interpretation of a non-significant result.

We did not find that umbilical artery FVW values were related to diabetic control as judged by glycosylated haemoglobin, but very few women were poorly controlled, and this observation is therefore limited. The association had been reported, using blood glucose as an index of glycaemic control, by Bracero *et al.* (1987) in a smaller series.

There were the expected relations between abnormal umbilical artery FVWs and antenatal fetal compromise and birthweight. However, more important in terms of clinical use is the ability to predict normality. Unfortunately our study demonstrates that, in diabetic pregnancy, abnormal non-stress tests and biophysical profiles can occur in the presence of a normal umbilical artery FVW. This is unlike the situation in uncomplicated intrauterine growth retardation or hypertension, where we have found normal FVWs to be highly predictive of normal antepartum fetal monitoring findings (Haddad *et al.* 1988a; 1988b) as have others (Gudmundsson & Marsal 1988; Burke *et al.* 1990).

There are two explanations for our findings. The first is that in these diabetic pregnancies, abnormal antenatal monitoring results have not reflected fetal compromise. Biophysical tests are influenced by maternal blood glucose levels (Teramo *et al.* 1983; Karineiemi *et al.* 1983) and fetal compromise is more difficult to define in diabetic pregnancy. The second reason may be the multifactorial nature of fetal compromise in diabetic pregnancy. Such compromise may not entirely be due to uteroplacental deficiency leading to chronically developing asphyxia, but may instead have an important metabolic component. Final deterioration, in a marginally compromised situation, may occur rapidly. This could occur in a macrosomic baby with a large placenta and this event may not be predictable by Doppler FVWs, which reflect vascular function of the placental bed (Giles *et al.* 1985; McCowan *et al* 1987). In support of this explanation there are already two reports of unexplained intrauterine death in diabetic pregnancies preceded by normal umblical artery FVWs 3 days before (Bradley *et al.* 1988; Tyrrel 1988). Similar failures to predict fetal death have been reported with other methods of fetal monitoring, particularly where diabetes has been poorly controlled (Barrett *et al.* 1981; Golde & Platt 1985; Miller & Horger 1985) and fetal compromise has been reported within a few days of a reactive non stress test (Teramo *et al.* 1983; Schmidt *et al.* 1980).

Doppler FVW analysis is an exciting development in fetal monitoring. The effect of diabetes is multifactorial, and while Doppler may yet prove to have value in diabetic pregnancy, this remains to be demonstrated. Abnormal FVWs may well be predictive of poor fetal outcome, particularly in the presence of established vascular disease, hypertension or relative growth retardation. However, the corollary may not be true, and we urge caution in placing reliance on normal Doppler studies in diabetic pregnancies until this situation becomes clear.

Acknowledgments

We are grateful for the skilled help of Sister Mary Compton and Miss Glenda White for making many of the recordings. We are grateful to Dr Robin Prescott for statistical advice.

References

Beattie R. B. & Dornan J. C. (1989) Antenatal screening for intrauterine growth retardation with umbilical artery Doppler ultrasonography. *Brit Med J* **298,** 631-635.

Barrett J. M., Salyer S. L. & Boehm F. H. (1981) The non stress test: An evaluation of 1000 patients. *Am J Obstet Gynecol* **141,** 153-157.

Bracero L., Shulman H., Fleischer A. *et al.* (1987) Umbilical artery velocity in diabetes and pregnancy. *Obstet Gynecol* **68,** 654-658.

Bradley R. J., Brudenell J. M & Nicolaides K. M. (1988) Chronic fetal hypoxia in diabetic pregnancy. *Brit Med J* **296,** 790.

Burke G , Smart B., Crowley P. *et al* (1990) Is intrauterine growth retardation with normal umbilical artery blood flow a benign condition? *Br Med J* **300,** 1044-1045.

Forbes J. F., Smalls M. J. & Cole S. K. (1982) *Centile Values of Birthweight for Gestational Age in Scottish Infants 1975–1979.* Social Paediatrics and Obstetrics Research Unit, University of Glasgow.

Giles W. B., Trudinger B. J. & Baird P. J. (1985) Fetal umbilical artery flow velocity waveforms and placental resistance: pathological correlation. *Br J Obstet Gynaecol* **92,** 31-38.

Golde S. & Platt L. (1985) Antepartum testing in diabetes. *Clin Obstet Gynecol* **28,** 516-527.

Gudmundsson S. & Marsal K. (1988) Umbilical and uteroplacental blood flow velocity waveforms in pregnancies with fetal growth retardation. *Eur J Obstet Gynecol Reprod Biol* **27,** 187-196.

Haddad N. G., Johnstone F D. & Chambers S. E. (1988a) Umbilical artery doppler waveform in pregnancies with uncomplicated intrauterine growth retardation. *Gynecol Obstet Invest* **26,** 206-210.

Haddad N. G., Johnstone F. D., Chambers S. E. *et al* (1988b) Umbilical artery Doppler flow velocity waveform analysis and the outcome of hypertensive pregnancies. *J Obstet Gynaecol* **9,** 9-13.

Hoskins P. R., Haddad N. G., Johnstone F. D. *et al* (1989a) The choice of index for umbilical artery Doppler waveforms. *Ultrasound Med Biol* **15,** 107-111.

Hoskins P. R., Johnstone F D., Chambers S. E. *et al.* (1989b) Heart rate variation of umbilical artery Doppler waveforms. *Ultrasound Med Biol* **15,** 101-105

Hoskins P. R., McDicken W. N., Johnstone F. D. *et al.* (1988) The determination of the presence of fetal apnoea using umbilical artery and umbilical vein Doppler waveforms. *Ultrasound Med Biol* **14,** 589-592.

Johnstone F. D., Haddad N. G., Hoskins P. *et al.* (1988) Umbilical artery Doppler flow velocity waveform. the outcome of pregnancies with absent end diastolic flow. *Eur J Obst Gynecol Reprod Biol* **28,** 171-178.

Karineiemi V., Forss M., Siegberg R. & Ammala P. (1983) Reduced short term variability of fetal heart rate in association with maternal hyperglycaemia during pregnancy in insulin-dependent diabetic women. *Am J Obstet Gynecol* **147,** 793-794.

Landon M. B., Gabbe S. G., Bruner J. P. & Ludmir J. (1989) Doppler umblical artery velocimetry in pregnancy complicated by insulin-dependent diabetes mellitus. *Obstet Gynecol* **73,** 961-965.

McCowan L. M., Mullen B. M. & Ritchie K. (1987) Umbilical artery flow velocity waveforms and the placental vascular bed. *Am J Obstet Gynecol* **157,** 900-902.

Manning F. A., Morrison I. & Lange I. R. (1985) Fetal assessment based on fetal biophysical profile scanning: Experience in 12 620 referred high risk pregnancies 1. Perinatal mortality by frequency and aetiology. *Am J Obstet Gynecol* **151,** 343-350.

Miller J. M & Horger E. D. (1985) Ante partum heart rate testing in diabetic pregnancy. *J Reprod Med* **30,** 515-518.

Pearce J. M., Campbell S., Cohen-Overbeek T. *et al* (1988) References ranges and sources of variation for indices of pulsed Doppler flow velocity waveforms from the utero placental and fetal circulation. *Br J Obstet Gynaecol* **95,** 248-256.

Schmidt P. L., Thorneycroft I. H. & Goebelsmann U. (1980) Fetal distress following a reactive nonstress test. *Am J Obstet Gynecol* **136,** 960-962.

Teramo K., Ammala P., Ylinen K. & Raivio K. O. (1983) Pathologic fetal heart rate associated with poor metabolic control in diabetic pregnancies. *Obstet Gynecol* **61,** 559-565.

Tyrrel S. N. (1988) Doppler studies in diabetic pregnancy. *Br Med J* **296,** 428

White P. (1965) Pregnancy and diabetes, medical aspects. *Med Clin North Am* **49,** 1015–1024.

Received 26 June 1990
Resubmitted 20 May 1991
Accepted 10 October 1991

British Journal of Obstetrics and Gynaecology
February 1992, Vol 99, pp. 141–143

FETAL AND NEONATAL MEDICINE

Jejunal atresia related to the use of methylene blue in genetic amniocentesis in twins

JOHAN G. VAN DER POL
HANS WOLF
KEES BOER
PIETER E. TREFFERS
Department of Obstetrics and Gynaecology
NICO J. LESCHOT
Department of Human Genetics
HUGO A. HEY
ANTON VOS
Department of Paediatric Surgery

The Academic Medical Centre
University of Amsterdam
The Netherlands

ABSTRACT

Objective To calculate the incidence of jenunal atresia in newborns in The Netherlands. To study the relation between the occurrence of jejunal atresia and genetic amniocentesis to determine a possible iatrogenic cause for the unexpected high incidence of this anomaly in twins.

Design Retrospective study.

Subjects Eighty-nine consecutive twin pregnancies in which amniocentesis had been performed for prenatal diagnosis. In 86 methylene blue solution had been used to mark the amniotic cavity that was punctured first.

Main outcome measure The occurrence of jejunal atresia in one of the two twin infants.

Results The incidence of jejunal atresia at birth in The Netherlands is estimated to be 1 in 14 000. This anomaly occurred in 17 out of 89 twin pregnancies (19%). In 15 of the 17 it was possible to determine which of the two children had been exposed to intra-amniotic methylene blue. In all 15 pregnancies, the infant exposed to the dye was suffering from jejunal atresia.

Conclusion A causal relation between the use of methylene blue in second trimester amniocentesis and the occurrence of jejunal atresia is strongly suggested. We recommend that no dyes should be injected into the amniotic sac.

Jejunal atresia is a rare congenital malformation of the small bowel. The incidence of this anomaly is reported to be in the range of 1 in 10 000 livebirths (Ravitch & Barton 1974; Safra *et al.* 1976). In studies of small bowel atresia twins did not have an increased risk compared with singletons (deLorimer *et al* 1969; Zerella & Martin 1976).

In the Centre of Paediatric Surgery in Amsterdam an unexpected high incidence of jejunal atresia in twins was recorded recently: 11 cases in 2·5 years (Moorman-Voestermans *et al.* 1990). The average age of the mothers at the time of delivery was 37 years. Only one of them was younger than 35. This drew our attention to a possible relation between genetic amniocentesis and jejunal atresia in twins. Only four of the twin pregnancies described by these authors were known to have had an amniocentesis, but this was known only if it was mentioned in the records of the paediatrician. The mothers were not questioned directly and the use of amniocentesis was not checked with centres for antenatal diagnosis.

No specific pattern of congenital malformations has been reported in several studies of amniocentesis in twins (Golbus *et al.* 1979; Elias *et al* 1980; Librach *et al.* 1984; Taylor *et al.* 1984; Pijpers *et al.* 1988) but, very recently, a letter concerning the risk of intestinal obstruction related to amniocentesis in twins was published (Nicolini & Monni 1990).

A possible relation between jejunal atresia and genetic amniocentesis in twins is the subject of this investigation.

Subjects and methods

Genetic amniocentesis in twins

Between 1 January, 1985 and 1 April, 1990, 1429 pregnant women underwent first trimester chorion villus sampling, and 4204 second trimester amniocentesis in the outpatient clinic of the Academic Medical Centre in Amsterdam. Of these 5633 pregnancies 89 (1·6%) involved a twin pregnancy. During the study period amniocentesis was the chosen diagnostic method for chromosomal analysis in twin pregnancies. The medical records of these 89 women and their infants were reviewed, with special attention to congenital malformations of the intestinal tract. The records of these children were compared with those of the Amsterdam Centre of Paediatric Surgery, and of the other centres of paediatric surgery in the Netherlands, to make sure that all cases of jejunal atresia were detected.

In none of the 89 women did the family history, obstetric history, use of drugs, or other data suggest either a specific common factor for an increased risk of intestinal tract anomalies.

Indications for amniocentesis were: advanced maternal age (≥36 years) in 78 women, recurrence risk of chromosomal abnormalities in eight, risk of neural tube defects in two, and congenital malformations, detected by ultrasound, in one

Correspondence: Dr J. G. van der Pol, Department of Obstetrics and Gynaecology, Academic Medical Centre, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.

woman. All amniocenteses were performed by experienced obstetricians under direct ultrasound guidance at approximately 16 weeks gestation (100–123 days).

In all cases the position of the two fetuses in relation to the septal membrane was recorded. Which of the two sacs was punctured first was recorded in the woman's record.

To be certain that the two samples of amniotic fluid were taken from two separate amniotic cavities, methylene blue was injected into the amniotic sac that was punctured first. In 86 of our 89 twin pregnancies between 1 and 2 ml of a 1% methylene blue solution in sterile water was used. In the other three women methylene blue was not used: once because the two amniotic sacs were clearly distinguished by ultrasound and in the other two women it was impossible to obtain amniotic fluid from both cavities, due to oligohydramnios in one of the sacs.

In our department of human genetics chromosomal analysis and determination of the alpha-feto protein level were performed on 174 and 176 amniotic fluid samples, respectively.

The incidence of jejunal atresia in The Netherlands

The incidence of jejunal atresia in The Netherlands was determined by an inquiry among all centres of paediatric surgery in the country, with special attention to the incidence in twins.

Results

Follow-up of genetic amniocentesis in twins

Of the 178 twin infants, 160 were liveborn and 18 were stillborn. Sixteen of the liveborn infants showed signs of small bowel obstruction and underwent operative therapy within a few days after birth. In all but one the obstruction was suspected prenatally between 26 and 34 weeks gestation after routine ultrasound assessment. In one baby the small bowel obstruction was discovered in the neonatal period. During operation one or more obstructions of the jejunal part of the small intestine were seen and resection followed by primary anastomosis was performed. In 13 of the 16 babies the atresias were multiple and mesenteric gaps were present. All children recovered with gradual resumption of a normal bowel function.

Microscopic examination of the resected specimens by the pathologist confirmed the clinical diagnosis: membranes, stenosis and atresias were found.

In the group of 144 liveborn infants that were not affected one congenital malformation was diagnosed: Jeune's syndrome (asphyxiating thoracic dysplasia).

In the group of 18 stillborn infants one well described case of jejunal atresia was present. Several weeks before the fetus died *in utero*, as a result of severe placental infarction combined with growth retardation, a massive dilatation of intestinal loops was seen on ultrasound. Multiple obstructions of the jejunum were found at autopsy.

In the group of stillborn infants four further cases of congenital malformation were diagnosed. One fetus with urethral obstruction, bladder distension, hydro-ureters and hydronephrosis, and one fetus with a large omphalocele. These infants died at 18 and 28 weeks gestation, respectively. The malformations were present before the amniocentesis took place. Selective feticide was performed on two fetuses after trisomy-21 was diagnosed by chromosomal analysis.

All affected twins were discordant for jejunal atresia. Thus, this anomaly occurred in 17 out of 89 pregnancies (19%), and in 17 out of 178 children (10%): 10 boys and 7 girls. Methylene blue had been used during the amniocentesis in all of the pregnancies. In retrospect it was possible to determine whether the affected child had been exposed to methylene blue in its amniotic cavity in 15 of the 17 cases. In eight pregnancies the twins were of non-identical sex which made it possible, after birth, to identify the child exposed to methylene blue and in seven the position of the fetuses and their relation to the septal membrane was recorded accurately during frequent routine ultrasound examinations, thus enabling identification of the two fetuses. In all 15 cases the infant exposed to methylene blue was the one suffering from jejunal atresia. All the infants with jejunal atresia showed a normal karyotype and amniotic fluid alpha-feto protein level.

The incidence of jejunal atresia in The Netherlands

Between 1 January, 1986 and 1 January, 1991 at total of 930 000 children were born in The Netherlands. In this period 67 newborns were treated for jejunal atresia in the paediatric surgical centres, where virtually all neonatal surgery of this type is performed. Thus, the incidence of this specific anomaly in the above mentioned period can be estimated to be 1 in 14 000 newborns. Twenty (30%) of the 67 affected children were one of a set of twins.

In 19 of the 20 pregnancies that resulted in the birth of a twin infant with jejunal atresia, second trimester amniocentesis had been performed and a dye had been used: methylene blue in 18, and indigo carmine in one case.

Conclusion and discussion

The incidence of jejunal atresia in The Netherlands is approximately 1 in 14 000; 30% of the affected infants are one of a set of twins. In most of the twin pregnancies leading to the birth of a child with atresia of the jejunum a second trimester amniocentesis had been performed (19 of 20). In 18 a methylene blue solution was used as a marker for the amniotic cavity that was punctured first.

A follow-up study of genetic amniocentesis in twins in our department showed that in 15 of the 86 infants that were exposed to methylene blue *in utero* an atresia of the jejunum occurred, and in two other cases of jejunal atresia the exposure to this dye was possible but could not be established definitely.

These findings strongly suggest a causal relation between the intrauterine exposure to methylene blue at approximately 16 weeks gestation and the occurrence of jejunal atresia. It is not clear how methylene blue has this harmful influence. A local toxic effect after ingestion of the dye by the fetus and concentration in the jejunum could be important but the clinical features of jejunal atresia suggest a vascular genesis for this malformation (Louw & Barnard 1955).

In vitro studies have demonstrated an indirect sympathicomimetic effect of methylene blue on mesenteric and other vessels that is caused by a release of noradrenaline and dopamine from sympathetic nerves (Soares-de Silva & Caramona 1988).

In the chicken embryo, temporary ischaemia of the intestine, after occlusion of the omphalo-mesenteric artery, is followed by multiple stenoses and atresias of the bowel (Tibboel *et al.* 1980). Thus, spasm of the mesenteric artery after oral intake of methylene blue by the fetus could be a possible explanation for our findings.

Several case histories describing unfavourable neonatal outcomes after intra-amniotic use of methylene blue in the third trimester of pregnancy have been published (Cowett *et al.* 1975; Serota *et al.* 1979; Crooks 1982; McEnerney & McEnerney 1983). These case histories mainly concerned haemolytic anemia of the newborn. Atresia of the small bowel associated with the use of methylene blue at 15–17 weeks gestation was reported very recently by Nicolini & Monni (1990).

Other dyes used for second trimester amniocentesis in twins also have side effects that might be potentially harmful to the fetus (Kennedy *et al.* 1968; Ng *et al.* 1976; Price *et al.* 1978; Fribourg 1981; Greenberg *et al.* 1983). In our study, only three of the 86 amniotic fluid samples obtained by the second puncture was dye stained and it is only in these three pregnancies that not having used a dye could have resulted in an incorrect prediction of the karyotype.

We recommend avoidance of the use of all dyes for intra-amniotic purposes, as we have done since 1 April, 1990. Today's sophisticated equipment allows amniocentesis under direct ultrasonic guidance and this considerably reduces the risk of puncturing the same amniotic cavity twice.

Acknowledgments

We are indebted to the paediatric surgeons, Professors N. M. A. Bax, C. Festen, G. Kootstra and J. C. Molenaar and to Dr R. P. Zwierstra for their assistance in collecting the data on jejunal atresia in The Netherlands, and we wish to thank Yvonne Melchers for her technical assistance.

References

Cowett R. M., Hakanson D. O., Kocon R. W. & Oh W. (1975) Untoward neonatal effect of intra-amniotic administration of methylene blue. *Obstet Gynecol* **48,** 74-75S.

Crooks J. (1982) Haemolytic jaundice in a neonate after intra-amniotic injection of methylene blue. *Arch Dis Child* **57,** 872-873.

deLorimer A. A., Fonkalsrud E W. & Hays D. M. (1969) Congenital atresia and stenosis of the jejunum and ileum. *Surgery* **65,** 819-827

Elias S., Gerbie A. B., Simpson J. L., Nadler H L., Sabbagha R. E. & Shkolnik A. (1980) Genetic amniocentesis in twin gestations. *Am J Obstet Gynecol* **138,** 169-174.

Fribourg S. (1981) Safety of intra-amniotic injection of indigo carmine (letter) *Am J Obstet Gynecol* **140,** 350-351.

Golbus M. S., Loughman W. D., Epstein C. J., Halbasch G. H., Stephens J. D. & Hall B. D. (1979) Prenatal genetic diagnosis in 3000 amniocenteses. *New Engl J Med* **300,** 157-163.

Greenberg F., Elsas N. T., Reidy J. A., Chen A. T. L. & Stone L. B. (1983) Dye use in twin gestations (letter). *Am J Med Genet* **14,** 395-396.

Kennedy W. F. Jr., Wirjoatmadja K., Akamatsu T. J. & Bonica J. J. (1968) Cardiovascular and respiratory effects of indigo carmine. *J Urol* **100,** 775-778.

Librach C. L., Doran T. A., Benzie R. J. & Jones J. M. (1984) Genetic amniocentesis in 70 twin pregnancies *Am J Obstet Gynecol* **148,** 585-591.

Louw J. H. & Barnard C. N. (1955) Congenital intestinal atresia: observations on its origine. *Lancet* **ii,** 1065-1067.

McEnerney J. K. & McEnerney L. N. (1983) Unfavourable neonatal outcome after intra-amniotic injection of methylene blue. *Obstet Gynecol* **61,** 35-37S.

Moorman-Voestermans C. G. M., Hey H. A. & Vos A. (1990) Jejunal atresia in twins. *J Ped Surg* **25,** 638-639.

Ng T. Y., Datta T. D. & Kirimli B. I. (1976) Reaction to indigo carmine. *J Urol* **116,** 132-133.

Nicolini U. & Monni G. (1990) Intestinal obstruction in babies exposed in utero to methylene blue (letter). *Lancet* **336,** 1258-1259.

Pijpers L., Jahoda M. G. J., Vosters R. P. L., Niermeyer M. F. & Sachs E. S (1988) Genetic amniocentesis in twin pregnancies. *Br J Obstet Gynecol* **95,** 323-326.

Price P. J., Suk W. A., Freeman A. E., Lane W. T., Peters R. L., Vernon M. L. & Huebner R. J. (1978) *In vitro* and *in vivo* indications of the carcinogenicity and toxicity of food dyes. *Int J Cancer* **21,** 361-367.

Ravitch M. M. & Barton B. A. (1974) The need for paediatric surgeons as determined by the volume of work and the mode of delivery of surgical care. *Surgery* **76,** 754-763.

Safra M. J., Oakley G P. & Erickson J. D. (1976) Descriptive epidemiology of small-bowel atresia in metropolitan Atlanta. *Teratology* **14,** 143-149.

Serota F. T., Bernbaum J. C. & Schwartz E. (1979) The methylene blue baby. *Lancet* **ii,** 1142-1143.

Soares-da-Silva P. & Caramona M. M (1988) Effects of methylene blue on the uptake, release and metabolism of noradrenaline in mesenteric arterial vessels. *J Pharm Parmacol* **40,** 534-538.

Taylor M B., Anderson R. L. & Golbus M. S (1984) One hundred twin pregnancies in a prenatal diagnosis program. *Am J Med Genet* **18,** 419-422.

Tibboel D., van Nie C. J. & Molenaar J. C. (1980) The effects of temporary general hypoxia and local ischamia on the development of the intestines: an experimental study. *J Ped Surg* **15,** 57-62.

Zerella J. T. & Martin L. W. (1976) Jejunal atresia with absent mesentery and a helical ileum. *Surgery* **80,** 550-553.

Received 12 July 1991
Accepted 4 November 1991

British Journal of Obstetrics and Gynaecology
February 1992, Vol. 99, pp. 144–149

FETAL AND NEONATAL MEDICINE

Maternal serum screening for Down's syndrome: the effect of routine ultrasound scan determination of gestational age and adjustment for maternal weight

N. J. WALD
H. S. CUCKLE*
J. W. DENSEM
A. KENNARD
D. SMITH
Department of Environmental and Preventive Medicine
Wolfson Institute of Preventive Medicine
St. Bartholomew's Hospital Medical College
Charterhouse Square
London EC1M 6BQ

ABSTRACT

Objective To investigate the effect of using a routine ultrasound estimate of gestational age and maternal weight adjustment on maternal serum alpha-fetoprotein (AFP), unconjugated oestriol (uE_3) and human chorionic gonadotrophin (hCG) levels in antenatal screening for Down's syndrome.

Design Women with a singleton pregnancy without Down's syndrome were screened using the three serum markers and an estimate of gestational age based on 'dates' (time since first day of the last menstrual period) and one based on an ultrasound scan examination was recorded together with maternal weight.

Setting Women attending the Homerton Hospital, Hackney, for their antenatal care between February 1989 and January 1990.

Subjects 2113 women with a singleton pregnancy without Down's syndrome.

Results The use of ultrasound to estimate gestational age (usually based on the biparietal diameter of the fetal skull) led to a significant reduction in the variance of each marker at a given week of pregnancy. The level of each marker was negatively associated with maternal weight, so that adjustment for weight also led to a reduction in variance. These data on gestational age and maternal weight, taken together with published data on pregnancies associated with Down's syndrome, indicate that the routine use of ultrasound to estimate gestational age will increase the detection rate from 58% to 67% while maintaining the false-positive rate at 5%, or reduce the false-positive rate from 5·7% to 3·1% while maintaining the detection rate at 60%. Routine maternal weight adjustment for the serum marker levels was much less useful, increasing the detection rate by about 0 5% for a given false-positive rate, or reducing the false-positive rate about 0·1% for a given detection rate.

Conclusion An ultrasound gestational age estimate available at the time of Down's syndrome screening confers a substantial advantage to screening performance with a further small benefit resulting from maternal weight adjustment, which is worth adopting if it can be done without difficulty or extra cost.

Antenatal screening for Down's syndrome using maternal serum alpha-fetoprotein (AFP), unconjugated oestriol (uE_3), and human chorionic gonadotrophin (hCG) can detect about 60% of affected pregnancies with a false-positive rate of 5% (Wald *et al.* 1988a). This performance can be achieved without using an ultrasound examination to estimate gestational age and without adjusting the values of the three serum markers for maternal weight. These refinements improve the performance of screening using maternal serum AFP alone (Cuckle *et al.* 1987) and they are likely to confer a similar benefit on screening using the three serum markers together. We performed a study to investigate this and to estimate the size of any benefit that may arise.

Subjects and methods

Among women who attended the Homerton Hospital, Hackney, for their antenatal care between February 1989 and January 1990, 2113 had a singleton pregnancy without Down's syndrome or a neural tube defect. All had been screened for Down's syndrome using the three serum markers, AFP, uE_3 and hCG. Of these, 2028 women (96%) had an estimate of gestational age based on 'dates' (time since the first day of the last menstrual period) and an estimate based on an ultrasound scan examination. In this paper, when a biparietal diameter was available (1865) this was used; otherwise a crown-rump length (61) or an abdominal circumference (102) was used. In each pregnancy gestational age was estimated from a log-linear regression of gestational age based on dates against the ultrasound measure. The log-linear fit was at least as satisfactory a fit to the data as other simple models. A maternal weight measurement was available for 2050 women (97%).

Correspondence: Professor N. J. Wald.
*Present Address Academic Unit of Obstetrics and Gynaecology, Institute of Epidemiology and Health Services Research, St. James's University Hospital, Leeds LS9 7TF.

Table 1. Median maternal serum AFP, uE_3, and hCG levels according to maternal weight

Maternal weight (kg)		No. of women	Median (MoM)		
Group	Median		AFP	uE_3	hCG
<50	47·1	172	1·09	1·09	1·13
50–	52·9	215	1·12	1·04	1·16
55–	57·5	366	1·04	0·99	1·11
60–	62·2	346	0·99	0·99	1·04
65–	67·1	290	0·93	0·95	0·92
70–	72·3	165	0·84	0·99	0·91
75–	77·1	129	0·83	0·89	1·00
≥80	88·2	206	0·80	0·87	0·82

MoM = multiple of the median for pregnancies of the same gestational age.

The median marker level was regressed on the median maternal weight, weighted by the number of women in the group; the regression equations were: (i) median $\log_{10}$ AFP = 0·24714 – 0·0040924 maternal weight; (ii) median $\log_{10}$ uE_3 = 0·12868 – 0·0021491 maternal weight; and (iii) median $\log_{10}$ hCG = 0·24932 – 0·0037924 maternal weight.

When assessing the performance of the screening tests, the analysis was restricted to those women who were tested between 15 and 22 completed weeks gestation: 1944 women when gestational age was estimated using dates and 1927 using scan of whom 1889 and 1872 respectively had a maternal weight measurement recorded.

Maternal serum AFP was measured by radioimmunoassay using reagents produced by the North East Thames Regional Health Authority, uE_3 was measured by a direct, non-extraction radioimmunoassay (Amerlex oestriol RIA kit, Amersham) and hCG by an immunoradiometric assay (Serono MAIA-Clone Kit calibrated to the first international reference preparation at a dilution of 1 in 500). The concentrations of the three serum markers were expressed in multiples of the median (MoM) for pregnancies of the same gestational age. For each marker medians were obtained by regression of the median level (y) on gestational age in days (x) using the function $\log y = a + bx$ for AFP and uE_3 and the function $y = a + b.e^{cx}$ for hCG. This followed previous practice except for uE_3 when $y = a + bx$ had been used before (Wald *et al.* 1988b): The new log function fitted at least as well.

The risk of an individual woman having a Down's syndrome term pregnancy was derived, as before (Wald *et al.* 1988a), from her age and univariate, bivariate and trivariate Gaussian frequency distributions depending on the number of serum markers used. With the accumulation of larger numbers it emerged that a log Gaussian distribution fitted uE_3 levels better than a Gaussian distribution and that the upper and lower boundary limits for the Gaussian fit of each variable were 0·3–3·3 MoM for AFP, 0·4–2·5 MoM for uE_3 and 0.2–5·0 MoM for hCG. Parameters of the unaffected distributions using dates and scan to estimate gestational age, with and without maternal weight adjustment, were derived from the present data set and the parameters of the Down's syndrome distributions were derived from our previous study. These parameters are given in the Appendix together with the detailed method of derivation. The corresponding Down's syndrome detection rates (proportions of affected pregnancies with positive results) and false-positive rates (proportions of unaffected pregnancies with positive results) were estimated from the new parameters as before (Wald *et al.* 1988a) except that a more recent period (1984–1988) was used for the maternal age distribution for England and Wales (Office of Population Censuses and Surveys, 1985–1990). The maternal age-specific risk of Down's syndrome term pregnancy was derived from the rate in livebirths (Cuckle *et al.* 1987). Whilst the rate is 2–3 times higher for pregnancies ending in stillbirth (Cuckle *et al.* 1991), this has little effect on overall risk and would not justify the complexity of allowing for it. The Appendix also gives the AFP parameters for neural tube defects, since most centres

Table 2. Median 10th and 90th centile of AFP, uE_3 and hCG (in MoMs) according to method of estimating gestational age (dates or scan—based mainly on biparietal diameter) and maternal weight (unadjusted or adjusted)

Serum marker	Method of estimating gestational age	Unadjusted for maternal weight				Adjusted for maternal weight			
		Median	10th (a)	90th (b)	(b/a)	Median	10th (a)	90th (b)	(b/a)
AFP	Dates	0·98	0·53	1·74	3·28	1·01	0·56	1·81	3·24
	Scan	0·99	0·57	1·74	3·05	1·04	0·61	1·76	2·89
uE_3	Dates	0·99	0·62	1·47	2·37	1·00	0·64	1·49	2·33
	Scan	0·99	0·70	1·40	2·00	1·01	0·72	1·42	1·97
hCG	Dates	0·99	0·49	2·14	4·37	1·00	0·50	2·08	4·15
	Scan	1·00	0·49	2·02	4·12	0·99	0·49	1·99	4·06

MoM = multiple of the median level for pregnancies of the same gestational age.

Table 3. Performance of Down's syndrome screening using maternal age with different combinations of AFP, uE_3 and hCG: detection and false-positive rates according to method of estimating gestational age (dates or scan—based mainly on biparietal diameter)

Serum marker:	AFP		uE_3		hCG		AFP & uE_3		AFP & hCG		uE_3 & hCG		AFP, uE_3 & hCG	
Gestation:	Dates	Scan	Dates	Scan	Dates	Scan	Dates	Scan	Dates	Scan	Dates	Scan	Dates	Scan
False positive rate (%)							*Detection rate (%)*							
1	18	18	23	30	26	27	25	33	30	34	32	40	35	45
2	24	24	31	37	34	35	33	40	39	43	41	48	44	54
3	28	29	36	42	39	41	38	45	45	50	46	54	50	59
4	32	33	40	46	44	45	42	49	50	54	51	57	54	63
5	35	36	43	49	47	48	45	52	54	58	54	61	58	67
6	38	38	46	51	50	51	48	55	57	61	57	63	61	69
7	40	41	48	53	53	54	50	57	60	64	59	65	63	71
8	42	43	50	55	55	56	53	59	62	66	61	67	65	73
9	44	45	52	57	57	58	55	61	64	68	63	69	68	75
10	46	47	54	59	59	60	56	63	66	70	65	71	69	77
Detection rate (%)							*False-positive rate (%)*							
20	1·3	1·2	0·7	0·3	0·6	0·5	0·6	0·2	0·4	0·2	0·3	0·1	0·2	0·1
30	3·4	3·3	1·8	1·0	1·4	1·3	1·6	0·8	1·0	0·7	0·8	0·3	0·7	0·2
40	7·0	6·6	4·0	2·6	3·1	2·9	3·5	2·0	2·1	1·6	1·9	1·0	1·5	0·6
50	12	12	8·0	5·6	6·0	5·6	6·9	4·3	4·0	3·1	3·9	2·3	3·1	1·5
60	20	19	14	11	10	10	12	8·4	7·2	5·6	7·3	4·8	5·8	3·1
70	30	29	24	20	17	17	20	15	12	9·8	13	9·6	10	6·3
80	43	42	39	34	29	28	33	27	21	17	23	19	18	13

conducting serum screening for Down's syndrome combine this with AFP screening for neural tube defects.

Results

Table 1 shows for AFP, uE_3 and hCG the association with maternal weight. All three markers decreased with increasing maternal weight and log-linear regression equations predicting the expected value of each marker from a given maternal weight fitted well (these are given in a footnote to the Table).

Table 2 shows, for each serum marker, the median, 10th and 90th centile values according to whether gestational age was based on dates or the ultrasound scan examination. The greater precision of estimating gestational age by scan resulted in a contraction in the spread of MoM values for each marker as indicated by the ratio between the 90th and 10th centile. Table 2 also shows the median, 10th and 90th centile values according to whether maternal weight adjustment was carried out. Maternal weight was adjusted for by dividing the observed MoM by that predicted for the maternal weight using the appropriate regression equation. The contraction in the spread of values associated with such an adjustment was small—less than that associated with using scan rather than dates to estimate gestational age. The small differences in the median values shown in Table 2 are due to chance.

Table 3 shows the estimated Down's syndrome detection rate corresponding to specified false-positive rates, and the false-positive rates corresponding to specified detection rates, using maternal age and different combinations of the serum

Table 4. Down's syndrome detection rate (DR), false-positive rate (FPR) and odds of being affected given a positive screening result (OAPR) using maternal age, AFP, uE_3 and hCG according to method of estimating gestational age (dates or scan—based mainly on biparietal diameter) and maternal weight (unadjusted or adjusted)*

	Dates and unajusted for weight			Dates and adjusted for weight			Scan and unadjusted for weight			Scan and adjusted for weight		
Risk cut-off level	DR (%)	FPR (%)	OAPR	DR (%)	FPR (%)	OAPR	DR (%)	FPR (%)	OAPR	DR (%)	FPR (%)	OAPR
1:100	41	1·6	1:30	41	1·6	1:30	51	1·6	1:24	51	1·6	1:24
1:150	48	2·7	1:44	49	2·8	1:43	57	2·6	1:35	58	2·6	1:34
1:200	54	3·9	1:56	54	4·0	1:56	62	3·6	1:44	62	3·6	1:44
1:250	58	5·2	1:68	59	5·2	1:68	65	4·6	1:54	66	4·6	1:53
1:300	62	6·4	1:80	62	6·4	1:79	68	5·6	1:63	69	5·5	1:62
1:350	65	7·6	1:91	65	7·6	1:90	71	6·6	1:71	71	6·5	1:71
1:400	67	8·8	1:101	68	8·8	1:100	73	7·5	1:80	73	7·5	1:79

*A result is positive if the risk of a Down's syndrome term pregnancy given the maternal age and the three marker levels is greater than or equal to the specified cut-off risk.

markers, and according to whether gestational age was based on dates or the ultrasound scan examination. When maternal age and all three markers were used the ultrasound estimation of gestational age increased the detection rate by 8–10% (the precise estimate depending on the false-positive rate) or reduced the false-positive rate by about one to two thirds. Maternal weight adjustment had a much smaller effect, so that, for example, using all three markers with gestational age estimates based on scan and adopting a 5% false-positive rate the detection rate increased by about 0·5%; alternatively adopting a 60% detection rate the false-positive rate reduces from 3·1% to 3·0%.

Table 4 shows, for specified risk cut-off levels using maternal age and all three serum markers, the estimated Down's syndrome detection rate, false-positive rate and odds of being affected given a positive result according to the method of estimating gestational age and whether adjustment for maternal weight is carried out. For example, at a risk cut-off level of 1:250 the odds of having a Down's syndrome term pregnancy given a positive result are 1:68 using dates without weight adjustment and 1:53 using scan with weight adjustment.

Discussion

Our results show that the routine use of an ultrasound examination to estimate gestational age can usefully improve the performance of serum screening for Down's syndrome. With maternal age and all three markers together it increased the detection rate from 58% to 67% while holding the false-positive rate at 5%. Alternatively it nearly halved the false-positive rate from 5·8% to 3·1% while holding the detection rate at 60%. Some ultrasonographers report gestational age estimates as a rounded number of weeks or even as a range (e.g., 16–17 weeks) instead of as a point estimate (e.g., 16 weeks 3 days). This imprecision is best avoided when ultrasound is used routinely since otherwise the performance of screening will be unnecessarily impaired.

The biparietal diameter is the ultrasound measure of choice in Down's syndrome screening since it is well tried and provides a reasonably unbiased estimate of gestational age in pregnancies associated with Down's syndrome (Cuckle & Wald 1987). Its use is also of particular advantage in AFP screening for spina bifida; it increases the detection rate for open spina bifida from an estimated 73% to 85% based on the parameters given in the Appendix Table 1, using an AFP cut-off level of 2·5 MoM at 17 weeks gestation. It does so because fetuses with spina bifida have, on average, a small biparietal diameter (Wald *et al.* 1980; Roberts & Campbell 1980) and so affected pregnancies tend to be attributed with a less advanced gestational age and hence a higher AFP value in MoMs. The femur length should not be used as it will reduce the detection rate for Down's syndrome, for the same reason; on average the femur is short in fetuses with Down's syndrome (Cuckle *et al.* 1989), and affected pregnancies will therefore be attributed a less advanced gestational age and less extreme MoM values for all three serum markers.

The advantage of adjusting the values of the three screening markers for maternal weight is only marginal, yielding an estimated increase of about 1% or less in the detection rate. While the benefit is small such an adjustment would still be worthwhile if maternal weight were being used to adjust AFP values in screening programmes for open neural tube defects. It might, in any case, be considered if the weight were routinely available.

Our study was based on a group of women, nearly all of whom had an ultrasound scan estimate of gestational age and a maternal weight determination as part of their routine antenatal care. The completeness of the data will have avoided selection bias influencing our results. Of the three serum markers the performance of uE_3 was improved most by the ultrasound estimate of gestational age. This arose because the concentration of uE_3 changes most with gestational age in relation to its spread of values (by nearly half a standard deviation each week compared to about a quarter for AFP and hCG). It was therefore the marker that was most subject to gestational age error.

Our results will apply generally if the ultrasound scan examination provides an unbiased estimate of gestational age. If, on average, it underestimates gestation, the risk cut-off level will be decreased; if it overestimates gestation they will be increased.

The results in this paper do not apply to women who have an ultrasound scan examination because of a positive Down's syndrome serum screening result based on dates. In such women, because of the effect of regression to the mean, use of the scan estimate of gestational age would not only reclassify many unaffected pregnancies as having negative results (i.e., reduce the false-positive rate) but also reclassify some affected pregnancies as having negative results (i.e., reduce the detection rate and give false reassurance to the women involved). The extent to which this practice would lead to false-negative results is at present unknown but the problem is best avoided by routinely performing a dating ultrasound scan examination, and entering the ultrasound scan estimate of gestational age (based on a biparietal diameter measurement) on the serum screening request card so that the estimate can be used directly in calculating the MoM values of the three serum markers.

Acknowledgments

We thank Rossana Stone and Muriel Kitau for performing the biochemical tests, our colleagues in the Obstetrics Department of St. Bartholomew's Hospital for their support, and Glenn Palomaki, George Knight and James Haddow for their comments.

References

Cuckle H. S & Wald N. J. (1987) The effect of estimating gestational age by ultrasound cephalometry on the sensitivity of alpha-fetoprotein screening for Down's syndrome *Br J Obstet Gynaecol* **94**, 274-276.

Cuckle H S., Wald N. J. & Thompson S. G. (1987) Estimating a woman's risk of having a pregnancy associated with Down's syndrome using her age and serum alpha-fetoprotein level. *Br J Obstet Gynaecol* **94**, 387–402

Cuckle H. S., Wald N. J., Quinn J., Royston P. & Butler L. (1989) Ultrasound fetal femur length measurement in the screening for Down's syndrome. *Br J Obstet Gynaecol* **96**, 1373-1378.

Cuckle H, Nanchahal K. & Wald N. (1991) Birth prevalence of Down's syndrome in England and Wales. *Prenat Diagn* **11**, 29–34.

Fourth Report of the UK Collaborative Study on Alpha-Fetoprotein in

Relation to Neural Tube Defects (1982) Estimating an individual's risk of having a fetus with open spina bifida and the value of repeat alpha-fetoprotein testing. *J Epidemiol Community Health* **36**, 87-95.

Office of Population Censuses and Surveys (1985–1990) *Birth Statistics*. Series FM1, nos. 11, 12, 15–17. HMSO, London.

Roberts A. B. & Campbell S. (1980) Small biparietal diameter of fetuses with spina bifida: implications for antenatal screening. *Br J Obstet Gynaecol* **87**, 927-928.

Wald N., Cuckle H., Boreham J. & Stirrat G. (1980) Small biparietal diameter of fetuses with spina bifida: Implications for antenatal diagnosis. *Br J Obstet Gynaecol* **87**, 219-221

Wald N. J., Cuckle H. S., Densem J. W. *et al* (1988a) Maternal serum screening for Down Syndrome in early pregnancy. *Br Med J* **297**, 883-887.

Wald N. J., Cuckle H. S., Densem J. W. *et al.* (1988b) Maternal serum unconjugated oestriol as an antenatal screening test for Down's Syndrome. *Br J Obstet Gynaecol* **95**, 334-341.

Received 18 February 1991
Accepted 18 June 1991

Statistical appendix: estimation of parameters shown in appendix tables

The analyses used $\log_{10}$ MoM values. Means were estimated by the median values, and standard deviations by the differences between the 90th and 10th centile values divided by 2·563. The correlation coefficient between two variables was estimated by the covariance divided by the two corresponding standard deviations. The covariance was calculated after any outliers 3·5 standard deviations or more from the estimated mean had been removed.

(1) *Unaffected pregnancies*

The parameters were estimated directly from the four sets of data described in this paper: gestational age based on dates or scan with or without maternal weight adjustment. Since the small differences in the median values (Table 2) for the four sets are largely due to chance we assumed that they were all 1·0 MoM. In the UK Collaborative AFP Study (Fourth Report of

Appendix Table 1. Mean maternal serum AFP, uE$_3$ and hCG ($\log_{10}$) levels in singleton pregnancies (between 15–22 completed weeks of gestation) without Down's syndrome or neural tube defects, in pregnancies with Down's syndrome, and mean AFP alone in pregnancies with neural tube defects

Pregnancy	Serum marker	Mean* ($\log_{10}$)
Unaffected	AFP, uE$_3$ & hCG	0·0000
Down's syndrome	AFP	−0·1427
	uE$_3$	−0·1411
	hCG	0·3023
Anencephaly	AFP	
15 weeks		0·6262
16		0·7510
17		0·8274
18		0·8554
19		0·8349
20		0·7660
21		0·6487
22		0·4830
Open spina bifida	AFP	
15 weeks		0·4581 [0·6134]
16		0·5579 [0·7132]
17		0·6063 [0·7617]
18		0·6034 [0·7567]
19		0·5491 [0·7044]
20		0·4434 [0·5987]
21		0·2864 [0·4417]
22		0·0779 [0·2333]
Closed spina bifida	AFP	0·0000 [0·1553]

*Values in parentheses based on gestation estimated from a biparietal diameter.

Appendix Table 2. Standard deviation (SD) and correlation coefficient (R) in affected and unaffected pregnancies according to method of estimating gestation (dates or scan—based mainly on biparietal diameter) and whether the serum values are adjusted for maternal weight

Pregnancy*	Parameter	Serum markers	Dates and unadjusted for weight	Dates and adjusted for weight	Scan and unadjusted for weight	Scan and adjusted for weight
Unaffected	SD	AFP	0·2022	0·1976	0·1910	0·1806
		uE$_3$	0·1460	0·1437	0·1184	0·1153
		hCG	0·2484	0·2419	0·2401	0·2372
	R	AFP-uE$_3$	0·2755	0·2321	0·1040	0·0586
		AFP-hCG	0·0723	0·0338	0·1749	0·1322
		uE$_3$-hCG	−0·1752	−0·2112	−0·0476	−0·0869
Down's syndrome	SD	AFP	0·2050	0·2004	0·1940	0·1838
		uE$_3$	0·1939	0·1922	0·1741	0·1720
		hCG	0·2740	0·2681	0·2665	0·2638
	R	AFP-uE$_3$	0·2154	0·1822	0·0823	0·0521
		AFP-hCG	0·1703	0·1405	0·2699	0·2392
		uE$_3$-hCG	−0·2548	−0·2819	−0·1839	−0·2106
Anencephaly	SD	AFP	0·3516	0·3490	0·3453	0·3397
Open spina bifida	SD	AFP	0·3556	0·3530	0·3493	0·3437

*For closed spina bifida the SD of AFP is taken to be the same as for unaffected pregnancies the UK Collaborative Study on Alpha-Fetoprotein in Relation to Neural Tube Defects 1982) gestation specific standard deviations of AFP were used. This is an unnecessary complexity; in the present study the standard deviations were similar at each week (e.g., by dates 0·1998, 0·1980, 0·1970, 0·2256, 0·2068, 0·2028, 0·2127 and 0·2896 in 170, 736, 520, 218, 133, 97, 49 and 21 pregnancies in each consecutive week).

(2) *Pregnancies with Down's syndrome*

The parameters were estimated indirectly from previously published data relating to 77 Down's syndrome and 385 unaffected pregnancies (Wald *et al.* 1988a) by calculating three factors: the difference in means between affected and unaffected pregnancies (DM), the difference in the variances (DV) and the difference in the covariances (DC). These factors were used to adjust the parameters for unaffected pregnancies estimated in 1 above. The mean was estimated by adding DM to the corresponding mean; standard deviations by adding DV to the corresponding standard deviation squared and taking the square root; correlation coefficients by adding DC to the corresponding covariances and dividing by the new standard deviations.

(3) *Pregnancies with neural tube defects*

The AFP parameters were estimated indirectly by deriving DM and DV from data on anencephalic, spina bifida and unaffected pregnancies in the UK Collaborative AFP Study (Fourth Report of the UK Collaborative Study on Alpha-Fetoprotein in Relation to Neural Tube Defects 1982). The means for anencephaly and open spina bifida had been published previously in 3-week gestational periods, but to avoid the 'jump' between periods we used a quadratic regression on the single week median from 15–19 weeks and the three week median from 20–22 weeks. For anencephaly the equation was

$$\log \text{AFP} = -7{\cdot}056 + 0{\cdot}875 \times \text{gestation} - 0{\cdot}0242 \times (\text{gestation})^2$$

and for open spina bifida

$$\log \text{AFP} = -7{\cdot}203 + 0{\cdot}896 \times \text{gestation} - 0{\cdot}0257 \times (\text{gestation})^2.$$

The mean and standard deviation of AFP for closed spina bifida were taken to be the same as for unaffected pregnancies. When scan based on the biparietal diameter was used the value of DM for spina bifida was increased to allow for a 43% increase in medians (Wald *et al.* 1980). To derive DV the standard deviation in affected pregnancies was based on the 10th and 90th centiles of the deviation of $\log_{10}$ MoM values from the regressed medians and the standard deviation in unaffected pregnancies was based on the published values at 16–21 weeks gestation.

British Journal of Obstetrics and Gynaecology
February 1992, Vol. 99, pp 150–152

GYNAECOLOGY

Survey of colposcopy service provided by genito-urinary medicine in England and Wales

OLWEN WILLIAMS
MARGARET BODHA
University Department of Genito-Urinary Medicine
Royal Liverpool Hospital
Prescot Street
Liverpool L7 8XP, UK
D. HICKS
Department of Genito-Urinary Medicine
Royal Hallamshire Hospital
Sheffield S10 2JF, UK
A. B. ALAWATTEGAMA
University Department of Genito-Urinary Medicine
Royal Liverpool Hospital
Prescot Street
Liverpool L7 8XP, UK

ABSTRACT

Objective To investigate the expansion of colposcopy services within genito-urinary medicine (GUM) in England and Wales since 1985.
Design Data collected by postal and verbal communication from 189 genito-urinary medicine clinics in England and Wales in January 1990.
Subjects Consultant and junior genito-urinary physicians practising colposcopy.
Main outcome measures Number of clinics providing colposcopy service; indication for colposcopy, treatment facilities available, waiting lists and training opportunities, compared with that in 1985.
Results Of the 189 genito-urinary medicine clinics contacted, 60 provided a colposcopy service and 55 of these returned completed questionnaires. There has been a 67% increase in the number of colposcopes in use and over 50% of clinics have the facilities to treat cervical pathology Waiting lists were minimal for both examination and treatment. Both men and women are examined with the colposcope for a variety of indications. At present, 52% of career grade GUM physicians practise colposcopy compared to 24% in 1985 and 94% of senior registrars compared with 42% in 1985 were in training or trained in colposcopy.

With increasing numbers of young women attending genito-urinary medicine (GUM) clinics with genital human papillomavirus (HPV) infection and abnormal cervical cytology (Alawattegama 1984, British Co-operative Clinical Group 1985) there has been an increase in the number of physicians interested in and practising colposcopy.

Hicks *et al* (1986) commented in his survey on colposcopy: ‘Colposcopy is enjoying a healthy prospect in GUM.’ We considered it logical, to ascertain the expansion that had occurred in colposcopy services provided by genito-urinary medicine clinics in England and Wales over the last 5 years, and to discuss the implications for the future.

Method

In January 1990, all genito-urinary clinics in England and Wales on the Department of Health list (1989 personal communication) were questioned by telephone as to whether or not they provided a colposcopy service. Of the 189 clinics contacted 60 gave a positive reply. A postal questionnaire was then circulated to the 60 clinics, of which 55 were returned completed.

Results

Staff

There were 163 consultants in genito-urinary medicine in England and Wales in September 1989 (DHSS personal communications) of whom 68 (42%) practised colposcopy compared with 35 (29%) of the 120 consultants in 1985. There has been a corresponding rise in other members of staff who are trained or in-training colposcopists.

Equipment

Within the 55 clinics resources varied considerably, depending on whether a diagnostic and referral or a diagnostic and treatment service was provided. There were 76 colposcopes in use, with a range of 1–6 per clinic compared with 42 in 1985, an increase of 67% over the last 5 years. Three clinics had access to equipment in the Department of Gynaecology. Video recorders, photographic equipment and teaching aids were available in 26 clinics. Forty clinics were in possession of a cryoprobe. However, only a minority used it for treatment of cervical pathology other than warts or ectropion. A ‘cold coagulator’ was operational in 27 clinics, a LLETZ loop diathermy in 8 and laser equipment in 10. Eleven clinics did not treat any lesions and had no treatment equipment. In nine departments the treatment facilities were shared with gynaecology.

Patients

The colposcope was being used to study both men and women by physicians in genito-urinary medicine. Most patients were ‘in house’ referrals, with only 12 clinics routinely, and 9 clinics occasionally, accepting outside referrals, such as those from general practitioners. The indications for colposcopy in women are listed in Table 2 and sites studied in men and women in Table 3. In one clinic it was policy to use the col-

---

Correspondence: Olwen Williams MRCP.

Table 1. Number of staff who were trained or in-training colposcopists in 1990 and 1985

	1990		1985	
Grade	Total *n*	Colposcopists* *n* (%)	Total *n*	Colposcopists *n* (%)
Consultant	163	68 (42)	120	35 (29)
Associate specialist	9	5 (55)	9	1 (11)
Senior registrar	36	34 (94)	31	13 (42)
Registrar	45	16 (35)	42	6 (14)
Senior house officer	22	4 (18)	21	3 (14)
Clinical assistant	NA	28	NA	10
Staff-grade doctors	1	1 (100)	0	

NA = not available.
*Results represent 55 clinics.

poscope for all women irrespective of the presenting complaint and cytology (primary colposcopy). (Moss personal communications).

Workload

The number of colposcopy sessions held within each clinic varied from 1 per month to 8 sessions per week (mean 2 per week). Six clinics did not have allocated colposcopy sessions. Three centres used the colposcope on an ad hoc basis in addition to the dedicated colposcopy sessions. The number of patients attending individual colposcopy clinics varied between 1 and 12 (mean 4) per session. In clinics where the service was well established, numbers seen in one week were as high as 60 (over 5 sessions).

Waiting lists

Clinics which were developing their service had no waiting list whilst those with a well established colposcopy service did. This was partly due to the 'snowballing' effect caused by follow-up colposcopy and treatment.

Table 4 shows the waiting time from referral to colposcopy in relation to the specific indication.

Management of histologically proven cervical abnormalities

Management policies varied from clinic to clinic. Of the 55 centres, 12 treated all lesions suitable for out-patient therapy within their own units, referring to the gynaecology department only those requiring in-patient therapy. Twenty-three centres referred all patients, whereas five referred CIN 2 and greater and 13 centres considered CIN 3 an indication for gynaecology referral. No data were available from two clinics. Waiting time for treatment was minimal, all lesions were treated within 6 weeks. No data were available regarding waiting time for patients referred to the gynaecologists for treatment. In 1985, 15 consultants were taking biopsies from the cervix and only three were treating CIN.

Table 2. Indication for colposcopy in women reported by 55 genito-urinary medicine clinics

Indication	No. of clinics with policy to colposcope
Abnormal cytology	53
Genital warts	
Cervix only	4
Other sites	27
Consort with genital warts	21
Herpes genitalis	9
Macroscopically abnormal 'suspicious cervix'	40
Multiple consorts	7
HIV antibody positive	1
No data available	2

Table 3. Sites examined with the colposcope in men and women reported by 55 genito-urinary medicine clinics

	No. of clinics	
Sites examined	Routinely *n*	Occasionally *n*
Cervix	55	0
Vulva	37	3
Vagina	31	2
Rectum or anus with or without proctoscope	3	6
Penis	16	8

Training

As colposcopy becomes an integral procedure within genito-urinary medicine facilities, it is essential that juniors are trained adequately. At present, in the 55 clinics, 34 senior registrars are trained or trainees in colposcopy, representing 94% of this grade along with 35% registrars and 18% of senior house officers.

Comments

Colposcopy is now widely practised in genito-urinary medicine clinics, without any gross fiscal restraints, on the basis that HPV may cause cervical cancer (Kitchener 1988). Genito-urinary physicians of either gynaecological or medical background have adopted colposcopy with enthusiasm. Their colposcopic practise had changed dramatically over the 5 years, from that of an observer to that of an operator actively treating CIN. Concurrently, interest in preinvasive lesions of the penis and anal region has prompted some clinicians to examine these sites with the colposcope. In a population of women with a

Table 4. Waiting time for colposcopy in relation to indication in women reported by 49 genito-urinary medicine clinics*

	No. of clinics with these waiting times (weeks)				
Indication for colposcopy	None	2	6	13	52
HPV/contact	15	12	14	6	2
Mild dyskaryosis	15	13	14	6	1
Moderate dyskaryosis	15	13	19	2	0
Severe dyskaryosis	22	17	10	0	0

*Six of the 55 responders provided no data.

high prevalence of dyskaroytic smears, the advantages of 'on site' colposcopy and treatment are numerous (Wilson *et al* 1988, Byrne *et al.* 1989), including increased patient acceptability, precolposcopy counselling, minimized waiting time and reduced default rate. Follow-up is facilitated by computerization of the service, access to health advisers, and the diminished need for referral to gynaecology. However, there has been no assessment of the cost effectiveness of the service.

The national cytological recall programme has resulted in general practitioners taking an increasing number of smears and this has increased the number of women requiring colposcopy. Pressure on the existing gynaecological colposcopy service may result in genito-urinary medicine physicians accepting external referrals. Liaison between genito-urinary physicians and gynaecologists is essential to improve and rationalize the service. So far, both specialities have worked apart, although the support from gynaecology is encouraging (Walker 1987). It would be logical to centralize the service, establishing joint clinics where all women requiring colposcopy were referred and examined by colposcopists of either gynaecological, genito-urinary medicine or other background. This would standardize the service, maximise the use of resources and provide facilities for training and research.

Training of junior staff is labour-intensive and this may result in a reduction in patient numbers per clinic and so increase waiting lists. At present, the role of staff-grade doctors and clinical assistants is particularly important to the stability of the service as, unlike the juniors, they do not rotate to other posts.

Training in colposcopy as a pre-requisite for accreditation for higher medial training in genito-urinary medicine is being sought (Alawattegama & Hicks 1991).

The debate as to whether to use ablative or excisional methods for treatment of CIN exists within genito-urinary medicine as it does within gynaecology. The management of CIN within genito-urinary medicine clinics is influenced by the outcome of research both by gynaecolgists (Duncan 1981; Jordan 1985; Prendiville 1989) and genito-urinary medicine physicians (Williams 1990; Edwards 1990).

There has been a significant expansion in the colposcopy service within genito-urinary medicine over the last 5 years. This has been reflected in the formation of the Northern Genito-Urinary Physicians Colposcopy Group, whose membership exceeds 100, with the aim of the maintaining high standards of colposcopy. We envisage further expansion in the future as more clinicians develop their skills and those of their juniors and see no objection to development of out-patient treatment facilities within genito-urinary medicine, provided standards are maintained and close liaison with gynaecology continues. Consequently more efficient use of equipment, provision of treatment facilities and acceptance of external referrals should follow.

References

Alawattegama A. B (1984) Screening for cervical intraepithelial neoplasia and cancer in the Sheffield STD clinic. *Br J Vener Dis* **60,** 117-120.

Alawattegama A B. & Hicks D. A. (1991) Should training in colposcopy be obligatory in higher specialist training in genito-urinary medicine? *Genitourin Med* **67,** 427.

British Co-operative Clinical Group (1985) Cervical cytology screening in sexually transmitted disease clinics in United Kingdom. *Genitourin Med* **63,** 40-43.

Byrne M. A , Taylor-Robinson D., Anderson M. A. C., Mason P. & Harris J. R. W. (1989) Value of colposcopy in sexually transmitted disease clinic based on first year's experience. *Genitourin Med* **65,** 42-45

Duncan I. D. (1981) Treatment of CIN by destruction 'cold coagulator'. In *Pre-clinical Neoplasia of the Cervix (Proceedings of the IX RCOG Study Group)* (Jordan J. A., Sharp F, Singer A., eds), Royal College of Obstetricians and Gynaecologists, London, pp. 197-204.

Edwards A., Hallam, N., Hart L. & Gray W. (1990) Diathermy loop excision for cervical intraepithelial neoplasia. Spring Meeting, MSSVD. Shanklin Isle of Wight.

Hicks D. A. & Bushell T. E. C. (1986) Colposcopy in genito-urinary medicine clinics. *Genitourin Med* **62,** 284.

Jordan J A., Woodman C. B. J., Myelotte M. J., *et al* (1985) The treatment of cervical intraepithelial neoplasia by laser vaporization. *Br J Obstet Gynaecol* **92,** 394-398

Kitchener H. C (1988) Does HPV cause cervial cancer? *Br J Obstet Gynaecol* **95,** 1089-1091.

Prendiville W. & Cullimore J. (1989) LLETZ, A new method of management for women with CIN. *Br J Obstet Gynaecol* **96,** 1054-1060.

Walker P., Singer A. (1987) Colposcopy: Who, when, where and by whom? *Br J Obstet Gynaecol* **94,** 1011-1013

Williams O., Bodha M. & Alawattegama A. B. (1990) The management of cervical intraepithelial neoplasia in a department of genito-urinary medicine. *Exp Clin Canc Research* **9,** 1.

Wilson J D., Hill A. S & Hicks D. A. (1988) Value of colposcopy in genito-urinary departments *Genitourin Med* **64,** 100-102.

Received 3 May 1991
Accepted 7 October 1991

British Journal of Obstetrics and Gynaecology
February 1992, Vol. 99, pp. 153–157

FERTILITY CONTROL

Gynaecologists' abortion practice

COLIN FRANCOME
Senior Lecturer in Sociology
Middlesex Polytechnic
The Burroughs
London NW4 4BT, UK

WENDY D. SAVAGE
Senior Lecturer in Obstetrics and Gynaecology
London Hospital Medical School
Whitechapel, London E1 1BB, UK

ABSTRACT

Objective To ascertain the relation between gynaecologists' opinions on the provision of abortion and the service provided by the Health Service in their district and to investigate the methods used for second trimester abortion.
Design and Setting A postal questionnaire sent three times to a 50% random sample of gynaecologists practising in the National Health Service (NHS) in 1989 in Great Britain.
Subjects 343 of 396 practising gynaecologists, 87% of those selected.
Main outcome measures Proportion of gynaecologists holding views or reporting practice.
Results Although only 11% actually performed abortions beyond 20 weeks, 57% approved later operations in cases of rape and 85% for a threat to the woman's health; only 47% approved late abortion for schoolgirls under 16 years. Dilatation and evacuation was used by only 1% of NHS gynaecologists even though from 13 to 16 weeks it is a safe and efficient method. Although Government statistics report that vacuum aspiration is used in over one third of second trimester abortions, this is technically unlikely and was not confirmed by this study. Less than 50% of abortions in England and Wales are performed in the NHS yet fewer than 40% of gynaecologists reported problems in providing an abortion service. Overall 21% thought they were providing abortions for over 90% of the women resident in their districts, whereas only 2% of districts achieve this proportion in their home regional health authority. Overall 60% supported separating abortion work from general gynaecology, and 45% would like regional abortion units. Only 27% supported fertility control acquiring the status of a subspecialty
Conclusions Accepting these suggestions would improve the service, reduce regional variations in provision, provide opportunities for research and could have an important effect in helping slow the world population increase.

There has been little research in the United Kingdom into gynaecologists' attitudes to abortion or about their actual practice. It is known that there are marked regional variations in National Health Service (NHS) provision and in the use of sterilization and surgical methods of abortion (Savage 1981; Munday *et al.* 1989). The proportion of abortions carried out on the NHS in the West Midlands, for example, has rarely exceeded 20%, whereas in the Northern Region it has always been over 80%. In 1989, the districts with the lowest proportion of NHS abortions were in Dudley and North and South Birmingham (2%) and the district with the highest proportion (96%) was in North Devon (OPCS 1990). The attitudes underlying these differences were investigated by Chamberlain (1980), who conducted interviews as part of the Wessex abortion survey. She found that some consultants had a negative attitude towards abortion. Allen (1981), in a study for the Department of Health and Social Security in 1977, commented that there was 'considerable lack of knowledge among professional respondents about the abortion services'. She found that 'most consultants said that they very rarely refused to perform an abortion, but it was obvious from interviews with GPs that they did not refer certain cases to certain gynaecologists'. Maresh (1979) found no relation between gynaecological sessions, or numbers of beds to explain the regional variation in abortion provision which has persisted for over 20 years. We therefore set out to find out the attitudes of individual gynaecologists and whether these influenced their practice.

Methods

The questionnaire consisted of two parts. The first was concerned with attitudes to abortion and contained a number of questions to enable comparisons to be drawn with the attitudes of the general public. It also included social factors such as age, sex and religious practice that we thought might influence attitudes. The second part addressed practice.

We drew a random sample of 405 gynaecologists from the Medical Directory and from information provided for us by the Royal College of Obstetricians and Gynaecologists, on recent consultant appointments. We estimated that this size, just under half of all consultants in Britain, would be large enough to ensure that the findings were valid. We subsequently found that nine gynaecologists had retired, leaving a sample of 396.

Correspondence: Mrs W D Savage.

Care was taken to ensure that the respondents were drawn in proportion to the number of consultants in each region.

The questionnaires were first posted in January 1989. We sent a second mailing in May and a third in September. In October telephone calls were made to non-responders. We assured gynaecologists that their replies would be kept confidential during analysis and that no individuals, hospitals nor districts would be identified.

After three mailings and telephone calls we obtained responses from 87% of the sample. Of the 343 replies, six merely answered that they had a conscientious objection to abortion. Thirteen gynaecologists completed only one side of the questionnaire and some respondents did not answer all the questions so the total responses for each question vary.

One factor affecting the validity of the results is whether those who did not respond differed from those who replied, as this could introduce bias. We found in our sample no signficant difference in response by age group. There is no breakdown of consultants by age group, but the proportion of responses we obtained reflected the theoretical numbers in each age group so any differential response is unlikely to cause bias. However, the regions are known to have wide differences in the percentage of abortions performed on the NHS with the West Midlands being the lowest in 1989 at 14%. So a low response from consultants in this and similar regions could have meant we were underestimating the opposition to abortion. However, there was no correlation between response rate and proportion of NHS abortions.

Results

Although 75% of the gynaecologists thought that the law should be changed to make it illegal to perform an abortion after 24 weeks almost a quarter did not agree that legislative change was necessary. Paradoxically, 77% thought that the legal limit should be 24 weeks or above and some mentioned that there should be exceptions to that limit. Following the passage of the Human Fertilization and Embryology Act (1990) the law has changed to limit abortions to 24 weeks but now specifically allows later abortions on the grounds of protecting the life of the mother or severe fetal abnormality. Of the respondents, 89% stated that their own personal limit for performing abortions, apart from risk to the life of the woman or severe fetal abnormality, was ≤20 weeks (Francome & Savage 1989).

Asked specifically about whether or not they approved of abortion in exceptional circumstances, there was considerable theoretical support for later abortions (Table 1). The results show that there is a disparity between the fact that many were unwilling to perform an abortion after 20 weeks, except for malformation or to save the woman's life, and yet would support the legal availability of later abortions for wider implications if someone else were willing to perform them. Although the results showed no significant difference between gynaecologists according to age or sex they indicated that Scottish respondents were more permissive.

Method of abortion after 13 weeks

A variety of methods are used to terminate a pregnancy after 13 weeks gestation so we asked an open-ended question as to what methods gynaecologists used, from 13 to 16 weeks and after 16 weeks. The results (Table 2) show that over 7% of gynaecologists who performed abortions after 16 weeks did not mention using a method between 13 and 16 weeks suggesting they delayed the procedure in order to induce abortion with prostaglandin. The proportion of gynaecologists using dilatation and evacuation, both before and after 16 weeks, was very low and contrasts with the situation in the non-NHS clinics in which vaginal methods are used in 65% of abortions between 13 and 19 weeks (Office of Population Censuses and Surveys (OPCS) 1990). None of the gynaecologists who answered our survey used vacuum aspiration alone in the second trimester, although this method is reported by OPCS from the notification forms as being used for 37% of abortions between 13 and 19 weeks. The replies did not allow us to ascertain what proportion of prostaglandin terminations are done using prostaglandin by the intra-amniotic and extra amniotic routes as the route of administration was rarely specified.

It is interesting that the synthetic prostaglandin analogue, gemeprost, which is relatively new to the market (and did not complete the abortion within 24 h in 20% of the women as reported by Cameron & Baird 1984) has become quite widely used. Hill and Mackenzie (1989) have shown that intra- and extra-amniotic routes are safe and effective and doubt whether these methods should be displaced by dilatation and evacuation or a new prostaglandin technique.

Problems with organization of an abortion service

Gynaecologists were asked 'How often do any of the following problems lead to difficulties in providing an abortion service in your hospital?' They were then asked about shortages of beds, operating time, nursing staff and attitudes of medical or nursing staff. The results are shown in Table 3.

The proportion of gynaecologists reporting difficulties in providing a service was remarkably low even though less than half of the abortions performed in England and Wales are pro-

Table 1. Attitudes to late abortion expressed by gynaecologists

		Attitude		
Reason for abortion after 20 weeks	No. of respondents	Approve (%)	Disapprove (%)	Neither (%)
Woman's health at risk	313	85	7	8
Risk of severe handicap	314	90	4	5
Pregnant from rape	311	57	26	16
Schoolgirl under 16	309	47	33	21

Table 2. Number of gynaecologists using various methods for second trimester abortion in England and Wales (E & W) and in Scotland (S), compared with abortion statistics from OPCS*

	No. of respondents				No. of abortions (OPCS)*	
	13–16 weeks		> 16 weeks		13–19 weeks	
Method of abortion	E & W	S	E & W	S	NHS	Non-NHS
PG pessary or route unspecified	68	16	99	18		
Gemeprost	43	6	45	5		
Extra-amniotic PG alone	–	–	70	7		
Extra-amniotic PC	47	6	16	–		
Intra-amniotic PG ± urea	–	–	7	5		
All PG procedures *n*	158	28	237	35	4041	2592
(%)	(60)	(76)	(86)	(81)	(47)	(26)
D & E	28	–	3	–		
D & E after cervical PG	11	1	2	1		
Vaginal surgical *n*	39	1	5	1	3901	6505
(%)	(15)	(3)	(2)	(2)	(45)	(65)
Various methods *n*	64	8	33	7	655	941
(%)	(25)	(22)	(12)	(16)	(8)	(9)
No. performing abortions	261	31	275	43		
No not performing abortions	14	1	21	1		
Method not stated but performed abortions > 16 weeks	21	6	–	–		
Total no. of respondents/abortions	296	44	296	44	8597	10038

*OPCS (1990) data for England and Wales from abortion statistics 1989.

Abbreviations PG = prostaglandin; D & E = dilatation and evacuation; NHS = National Health Service.

vided by the NHS. The Scottish gynaecologists were less likely to have difficulties with beds and operating time but more likely to experience problems with attitudes of the nursing staff. The few gynaecologists who reported having problems every week because of shortage of beds, operating sessions and nursing staff mostly practised in the four Thames Regions.

Gynaecologists' perceptions of the service provided in their district

The proportion of abortions provided by the NHS in the home regional health authority (RHA) for the women resident in each district varied in 1988 from 2% to 95% and we wished to assess how aware gynaecologists were of the situation in their own district. We asked: 'What proportion of abortions do you estimate are carried out by the NHS in your district?' We compared their estimate with the data published by OPCS for England and Wales (Table 4).

Table 3. Factors affecting provision of an abortion service

Factor	No. of replies	Percentage of replies (%)				
		Never	Yearly	Monthly	Weekly	Other
Shortages of						
Beds	321	60	14	11	12	3
Operating time	322	60	11	11	15	3
Nursing staff	314	76	9	6	6	3
Attitudes of						
Nurses	315	68	16	9	3	4
Doctors	312	65	17	7	6	5

This analysis is confined to the 231 replies from England and Wales that gave a numerical estimate. In addition, 18 did not respond to this question, 24 said they did not know the proportion, 15 considered that the majority of abortions were done within the NHS whereas 8 thought it was a minority.

Almost half (45%) of those who gave a numerical estimate thought that over 70% of abortions were done within the NHS in their district with a fifth (21%) estimating over 90%. In reality, in England and Wales, only 17% of NHS districts (16% of our respondents) provide over 70% of the abortions for the locally resident women, with only 2% providing over 90%. Conversely only 23% thought their districts provided ≤40% of the abortions whereas in reality 49% provided this proportion. These figures show clearly that gynaecologists are not aware of what is happening locally.

Views on abortion as a part of gynaecology

We asked gynaecologists whether they favoured separating abortion from general gynaecology, setting up regional abortion units and making fertility control, contraception, sterilization and abortion, a subspecialty of obstetrics and gynaecology. The results are given in Table 5. Scottish gynaecologists were less likely to agree that abortion should be separated from general gynaecology (37% *vs* 64%) and that there should be a subspecialty of fertility control (11% *vs* 29%) although they were similarly divided about regional abortion units for second trimester operations. Women gynaecologists were significantly less likely to want regional units (26% *vs* 50%) but did not differ on the other questions.

Table 4. Gynaecologists' estimated proportions of abortions performed within the National Health Service (NHS) for women resident in their own district in 1989 (England and Wales) compared with OPCS data*

Estimated proportions of abortions done in respondent's district in the NHS		OPCS data for abortions in the NHS*	
Abortions (%)	No. of estimates (*n* = 231) *n* (%)	Abortions (%)	Proportion of districts (%)
≤20	25 (11)	≤ 20	22
21–40	28 (12)	21–40	27
41–50	42 (18)		
51–60	20 (9)	41–60	26
61–70	12 (5)		
71–80	23 (10)	61–80	15
81–90	32 (14)	81–90	11
91–100	49 (21)		
Other replies			
Don't know	24		
Majority of abortions	15		
Minority of abortions	8		

*Percentages for England and Wales derived from OPCS (1989) *Abortion Statistics 1988*, Series AB No. 15, HMSO.

Discussion

Gynaecologists tended to think that they were providing more of the abortion service than was in fact the case. There was a surprising lack of awareness by many respondents about their failure to provide an adequate service. In 1989 only 41% of abortions were performed in the NHS, and another 5% on an agency basis (OPCS 1990). We feel that the target should be at least 90%. One area which provided a good service found that only 4% of women paid to have their operations.

Gynaecologists did not appear to think that a shortage of clinical resources was a limiting factor, and their perception that they were providing most of the abortions may be because they operate on most of those referred to them. Allen (1981) found that general practitioners selected the women they referred to gynaecologists on the basis of previous performance in agreeing to terminate according to his or her own limited list of indications. Clarke *et al* (1983) found that if NHS facilities were inadequate general practitioners referred those who were able to pay to the charitable or private sector. In addition one third of women bypassed their general practitioners because they perceived the non-NHS service to be faster or more sympathetic. A more positive action towards abortion is needed as well as increased funding if the percentage of terminations performed in the NHS is to be increased. In some districts agency arrangements may be a useful short term solution.

Studies from the USA have shown that dilatation and evacuation is a safer method of midtrimester abortion up to 20 weeks than intra-amniotic methods, yet this method has not been used widely within the NHS in Britain (Cadesky *et al.* 1981; Cates & Grimes 1981). For years the OPCS figures have recorded vacuum aspiration as a method used in one third of abortions from 13 to 19 weeks and even in 2% from 20 weeks, when this is known to be impossible. The gynaecologists did not list vacuum aspiration as a method that they used which raises questions about the accuracy and value of this aspect of the OPCS data for this period. However, the new notification form contains an appropriate list of methods and this should allow this error to be corrected. Twenty-one (7%) of gynaecologists apparently delayed the operation if the woman presented between 13 and 15 weeks to use a nonsurgical method after 16 weeks. This is known to increase the risk to the woman (Alberman & Dennis 1984). Dilatation and evacuation requires exercising or teaching a surgical skill personally whereas the use of gemeprost can be delegated to a relatively inexperienced trainee, this may explain why dilatation and evacuation is not widely used and the rapid increase in the use of gemeprost.

Considerable interest was shown in the idea that abortion should be separated from general gynaecology and almost half the respondents felt that regional abortion units would be appropriate for second trimester operations. The arguments for these changes in the provision of abortion are that it would be easier to ensure that those with a conscientious objection to abortion did not have to take part in this work in any way, and that it would be easier to provide a service sympathetic to women's needs (Savage 1990). The persisting regional vari-

Table 5. Organization and status of abortion services

		Percentage of replies (%)			
	No. of replies	Yes	No	Don't know	Other
Separate from general gynaecology	330	60	37	2	1
Regional abortion units	332	45	43	8	3
Subspecialty fertility control	329	27	62	9	2

ations in provision could probably be overcome if individual gynaecologists could opt-out of a service they do not wish to provide.

Every junior gynaecologist without a conscientious objection to abortion must be trained in termination methods. In regional abortion units it would be possible to train those who wished to learn to use the techniques necessary to do these operations safely. This might reduce the higher morbidity of NHS operations compared with those done in the non-NHS clinics (Frank *et al.* 1985) as a minority of trainees would become experts. As two-thirds of trainees at registrar level are from the Third World the creation of a subspecialty of fertility control or community gynaecology, i.e., contraception, sterilization and abortion, might be the way to create a framework for training which would help us to attack the world population problem in the next decade. According fertility control the status of a subspecialty should increase recruitment, and improve the possibilities for research into contraception and abortion. Putting the responsibility for administration, training and planning of services under these consultants should improve services and provide an example for those wishing to introduce fertility control methods in their own countries, adapted to suit the local circumstances. There are probably sufficient gynaecologists sympathetic to this idea for the Royal College of Obstetricians and Gynaecologists to consider it.

Acknowledgments

We would like to thank Sheila Hillier, PhD, who commented on the questionnaire design, Mark Anniss and Michelle Cowdray for help with mailing and data analysis, and the gynaecologists who helped us obtain a high response rate.

References

Alberman E. & Dennis J. (eds) (1984) *Late Abortions in England and Wales, Report of a National Confidential Study*, RCOG, London.

Allen I. (1981) *Family Planning Sterilization and Abortion Studies*, PSI, London.

Cadesky K. I , Ravinsky E. & Lyons E. R. (1981) Dilatation and evacuation: A preferred method of midtrimester abortion. *Am J Obstet Gynecol* **139**, 329-332.

Cameron I. T & Baird D. T. (1984) The use of 16, 16-dimethyl-trans Δ^2 prostaglandin E_1 methyl ester (gemeprost) vaginal pessaries for the termination of pregnancy in the early second trimester. A comparison with extra-amniotic prostaglandin E_2. *Br J Obstet Gynaecol* **91**, 1136-1140.

Cates W. & Grimes D. A. (1981) Morbidity and mortality of abortion in the US In *Abortion and Sterilization* (J. Hodgson, ed), Academic Press, London, Sydney, Toronto, pp. 159-165.

Chamberlain A. (1980) Consultant gynaecologists and attitudes towards abortion. *J Biosoc Sci* **112**, 407-410.

Clarke L , Farrell C. & Beaumont B. (1983) *Camden Abortion Study.* British Pregnancy Advisory Service Anstey Manor, Solihull.

Francome C. & Savage W D. (1989) Gynaecologists' attitudes to abortion. *Lancet* **ii**, 1323-1324.

Frank P. I., Kay C. R., Wingrave S. J., Lewis T L. T., Osborne J. & Newel C (1985) Induced abortion operations and their early sequelae: joint study of the RCGP and the RCOG. *J R Coll Gen Pract* **35**, 175-180.

Hill N. C. W & Mackenzie I. Z. (1989) 2308 second trimester terminations using extra-amniotic and intra-amniotic prostaglandin E_2: an analysis of efficacy and complications. *Br J Obstet Gynaecol* **96**, 1424-1431.

Maresh J. A. (1979) Regional variation in the provision of abortion services *Fertil Contracept* **3**, 41-48.

Munday D., Francome C. & Savage W. D. (1989) Twenty one years of legal abortion. *Br Med J* **298**, 1231-1234.

Office of Population Censuses and Surveys (1989) *Abortion Statistics Series AB 15, 1988*, HMSO, London.

Office of Population Censuses and Surveys (1990) *Abortion Statistics Series AB 16, 1989*, HMSO, London

Savage W. D. (1981) Abortion and sterilization—should the operation be combined? *Br J Family Planning* **7**, 8-12.

Savage W. D. (1990) Social Services Committee: Abortion Act 1967 'Conscience Clause' Minutes of Evidence. Wednesday, 21 March 1990, HMSO, London.

Received 26 July 1991
Accepted 11 September 1991

British Journal of Obstetrics and Gynaecology
February 1992, Vol. 99, pp. 158–166

CASE REPORTS

Radical exenterative surgery as the treatment for perineal intraepithelial neoplasia

R. A. F. CRAWFORD
J. H. SHEPHERD
T. JOBLING
Department of Gynaecology
C. R. WOODHOUSE
Department of Urology
N. BREACH
Department of Plastic Surgery
The Royal Marsden Hospital, Fulham Road, London SW3 6JJ

Case report

A 46-year-old woman presented to our hospital in 1988 with extensive, grossly symptomatic intraepithelial disease of the lower genital tract and perineum of more than 12-years' duration.

At the age of 34 she had been treated by her local hospital for perineal and cervical warts with diathermy. In 1979, she had a total abdominal hysterectomy for a micro-invasive squamous cell carcinoma of the cervix. In 1983, she was noted to have vaginal intraepithelial neoplasia (VAIN) on follow-up vault smears and was treated with a 5-day insertion of caesium-137. Following this treatment she suffered radiation vaginitis, which was treated with vaginal cream containing conjugated oestrogens (Premarin). In 1986, laser vaporization was used to treat recurrent dysplasia of the vaginal vault. In 1987, a 5-fluoro-uracil cream was applied for 4 weeks because of severely dyskaryotic smears associated with VAIN, proved by biopsy. Subsequent to this treatment, she developed severe vulval discomfort and pain, superficial dyspareunia and dysuria which persisted up to the time of radical surgery. In 1988, a further attempt at laser ablation was made. However, when it became clear that the patient had severe persistent dyskaryosis both in the vagina and on the vulva with intractable pruritis and discharge, a referral for radical surgery was made.

In 1989, the extensive perineal field change was confirmed and urethral dysplasia was discovered. The anus and rectum, however, were spared from this dysplastic process. Operative treatment consisting of vulvectomy, colpectomy and urethrectomy was therefore planned, with the aim of constructing a neo-vagina and continent conduit to the bladder, and covering the skin defect with a myo-cutaneous flap. At surgery, histological examination of a frozen section of the tissue margin at the bladder neck showed invasive squamous carcinoma. In view of this, a cystectomy and pelvic lymphadenectomy were performed. Reconstruction was accomplished with a caecal Mitrofanoff neo-bladder using the appendix as a catheterizable conduit, an isolated ileal segment as neo-vagina, while primary skin cover was achieved using a rectus abdominis myocutaneous flap.

Histology showed extensive carcinoma in-situ in the vagina, vulva and urethra, with a focus of invasive squamous carcinoma below the bladder base.

More than a year after her operation, the patient was well and asymptomatic with no sign of recurrence. She had resumed intercourse, which had been impossible for more than 2 years. The perineum was well healed and the ileal vagina had a reasonable capacity. Colposcopy showed no epithelial atypia. The reconstructed urinary diversion was continent.

Discussion

Intraepithelial neoplasia of the genital area can be multifocal and may even affect the lower urinary tract. Severe simultaneous dysplasia in the vulval (Chafe *et al.* 1988), vaginal (Audet-Lapointe *et al.* 1990) and urethral regions, however, appears to be rare and has not been reported previously.

Its apparent low malignant potential, minimal symptomology and occurrence in the younger age group of patients has encouraged a conservative approach to treatment (Shafi *et al.* 1989). Laser ablation or other excision techniques, superficial chemotherapy or even radiotherapy should be tried initially. It should be remembered that although the risk for malignant progression is unknown, it is undoubtedly present and higher in patients who have extensive intraepithelial field changes such as our patient and careful long term surveillance with colposcopy and biopsy must be kept on all areas in the lower genital tract including the urethra and anus.

However, in these rare and difficult cases of persistent severe and symptomatic disease, the radical surgical and modern reconstructive techniques on offer in gynaecological oncology units allow further scope for treatment and, by aiming to retain both sexual function and urinary continence, can succeed in alleviating a debilitating condition and enhancing the patient's quality of life.

References

Audet-Lapointe P., Body G., Vauclair R., Drouin P. & Ayoub J. (1990) Vaginal intraepithelial neoplasia. *Gynecol Oncol* **36**, 232-239.

Chafe W., Richards A., Morgan L. & Wilkinson E. (1988) Unrecognized invasive carcinoma in vulvar intraepithelial neoplasia (VIN). *Gynecol Oncol* **31**, 154-162.

Shafi M. I., Luesley D. M., Byrne P, Samra J. S., Redman C. W., Jordan J. A. & Rollanson T. P. (1989) Vulval intraepithelial neoplasia—management and outcome *Br J Obstet Gynaecol* **96**, 1339-1344.

Received 3 May 1991
Accepted 12 September 1991

Correspondence: Dr R Crawford, Obstetric Department, University College Hospital, Huntley Street, London WC1E 6AU

British Journal of Obstetrics and Gynaecology
February 1992, Vol. 99, pp. 159–160

Resolution of pre-eclampsia following intrauterine death of one twin

P. SARHANIS
Registrar
D. H. O. PUGH
Consultant

Department of Obstetrics and Gynaecology, East Glamorgan General Hospital, Pontypridd CF38 1AB

Case report

A 34-year-old woman in her fourth pregnancy attended the antenatal booking clinic at 18 weeks gestation. She had had three previous normal deliveries at term and had developed hypertension and proteinuria in all of them. All of the pregnancies were with the same partner. Her last menstrual period was on 25 March 1990 and a routine ultrasound scan confirmed the presence of a twin pregnancy, in accordance with her dates. The blood pressure on booking was 140/80 mm Hg and urinalysis was negative. A repeat ultrasound scan at 24 weeks confirmed appropriate growth, with an anterior and a posterior placenta. Each fetus had a separate amnion and chorion. At 27 weeks she was admitted to hospital by the community midwife because of a blood pressure of 150/100 mm Hg and (++) of protein in the urine (Ames reagent strips). An ultrasound scan showed average growth for twin A, but the biparietal diameter and abdominal circumference measurements of twin B were unchanged from those at 24 weeks, indicating a failure of intrauterine growth.

Routine investigations showed slightly elevated uric acid levels (0·43 mmol/l), an increased proteinuria and a creatinine clearance of 78 ml/min.

Over the following week, her blood pressure remained 140–150/95–105 mm Hg and proteinuria persisted. The investigations were repeated with similar results. She had bilateral ankle and tibial oedema and occasional frontal headaches, without visual disturbances or hypereflexia. Both fetal hearts remained audible.

An ultrasound scan one week after admission, at 28 weeks gestation, showed that the growth of twin A had been sustained, but twin B was dead. Doppler studies of the umbilical artery of the surviving twin showed a normal waveform.

The blood pressure decreased gradually until, by the end of the following week, it had returned to that recorded at the first antenatal examination. It remained at this level thereafter. The proteinuria and oedema resolved. The previous blood and urine investigations were repeated weekly, with particular attention to platelet count, fibrinogen and fibrinogen degradation products levels, to detect any consumptive coagulopathy but all remained within normal limits. Further investigations included a glucose tolerance test, the estimation of HbA_{1c}, and screening for lupus anticoagulant, anticardiolipin antibodies and virus infections. No abnormal results were obtained.

The woman remained in hospital and the fetus was monitored daily with cardiotocograms and twice weekly with biophysical profiles and Doppler studies of the umbilical artery flow. Growth of the surviving twin continued on the ultrasound scan until 33 weeks gestation. Thereafter the biparietal diameter and abdominal circumference remained unchanged at 34 and 35 weeks. In view of this and the increasing risk of consumptive coagulopathy, it was decided, after discussion with the mother, to deliver her at 35 weeks and 4 days by elective lower segment caesarean section. Twin A was a 2140 g female with Apgar scores of 8 and 10 at 1 and 5 min respectively. Twin B was a 560 g macerated female without gross abnormalities or evidence of cord accident. The presence of two chorionic sacs and two separate placentas was confirmed. The placenta of twin A weighed 310 g and that of twin B 290 g.

A postmortem examination of the dead fetus detected no external or internal malformations. Chromosome studies were not possible because of the marked autolysis. Histological examination of both placentas and cords showed no abnormality.

The mother left hospital 6 days after the birth and had no complications. The baby made good progress and was discharged a week later.

Discussion

The antepartum death of one twin is an uncommon occurrence. It has been estimated that the frequency of such an event varies from 0·5%–6·8% of all twin deliveries (Enbom 1985). Twin gestation is associated with increased perinatal mortality and morbidity. One of the complications which often accompanies twin pregnancies and contributes to this increase in mortality and morbidity is pre-eclampsia. The above is an unusual case of twin gestation complicated by pre-eclampsia and intrauterine death.

A limited number of twin pregnancies with antepartum death of one twin have been reported. The causes include congenital abnormalities, intravascular coagulopathy, cord and placental accidents and pre-eclampsia (Enbom 1985).

The incidence of severe proteinuric hypertension in twin pregnancies has been reported as 11% (MacGillivray 1983). In our patient there is great interest in the resolution of the symptoms and signs of pre-eclampsia after the intrauterine death of twin B. Despite the death of twin B, the pregnancy continued safely for a further 7 weeks, with close monitoring of twin A. Pre-eclampsia appears to have played a key role in the death of twin B. It is of interest that the pre-eclampsia did not appear to influence the growth of twin A and resolved completely after the fetal death. It appears that the condition was associated with and affected only twin B at that stage of the pregnancy. As the twins were probably dizygous, it is likely that a genetic factor expressed by the fetus only, or by the fetus and the mother predisposed our patient to pre-eclampsia. This supports the theory that severe pre-eclampsia is due to recessive factor (Cooper & Liston 1979), either single or multifactorial. This

Correspondence: Dr P. Sarhanis, Registrar, Department of Obstetrics and Gynaecology, Stepping Hill Hospital, Stockport SK2 7JE.

patient suggests a fetal or fetal and maternal genotype hypothesis rather than a maternal genotype hypothesis only (Sutherland *et al.* 1981). If the genetic factor involved the mother only, the death of one twin should not have resulted in the resolution of the abnormal signs.

References

Cooper D W. & Liston W. A. (1979) Genetic control of severe pre-eclampsia *J Med Genet* **16,** 409-416.

Enbom J. A. (1985) Twin pregnancy with intrauterine death of one twin. *Am J Obstet Gynecol* **152,** 424-429.

MacGillivray I. (ed) (1983) Pre-eclampsia in twin pregnancies. *Pre-eclampsia; the Hypertensive Disease of Pregnancy.* Holt-Saunders, Eastbourne.

Sutherland A., Cooper D. W. *et al.* (1981) The incidence of severe pre-eclampsia amongst mothers and mothers in-law of pre-eclamptics and controls. *Brit J Obstet Gynaecol* **88,** 785-791.

Received 17 May 1991
Accepted 11 September 1991

British Journal of Obstetrics and Gynaecology
February 1992, Vol. 99, pp. 160–161

Retroperitoneal abscess complicating a normal delivery

P. N. SHAH
Registrar

V. A. RANE
Registrar

A. S. MOOLGAOKER
Consultant

Department of Obstetrics and Gynaecology, Basingstoke District Hospital, Aldermaston Road, Basingstoke, Hants

Case Report

A 16-year-old girl was admitted as an emergency 23 days postpartum. Her antenatal period had been uncomplicated. At 36 weeks gestation, following a labour lasting 5½ hours she had a normal delivery at another hospital of a live male infant weighing 2800 g. Delivery was in the lithotomy position, her legs being supported by two attendants. She experienced no pain or backache during the antenatal course and felt nothing untoward happen during labour or delivery. Her perineum was intact but a lateral vaginal wall tear was sutured under local anaethesia with her legs supported on lithotomy poles. The blood loss at delivery was less than 100 ml. By the next day she developed low backache and pain in the region of the left hip which then spread to the left loin. She had no bowel or urinary symptoms. An ultrasound and pelvic X-ray the next day showed no abnormality and urine culture revealed no infection. Her haemoglobin was 10·2g/dl (pre delivery 11·7). She became withdrawn with continued pain in the left hip and was seen by a rheumatologist who could find no abnormality. She was treated with physiotherapy on a presumed diagnosis of 'muscle spasm' and was allowed home a week post delivery but had to use a walking frame in order to get about.

After going home the pain in the left hip progressively became worse, she was unable to walk without assistance and physiotherapy was not helping. She was therefore admitted. On admission she looked pale, had a blood pressure of 80/40 mmHg and was apyrexial. She was unable to lie on her back or on her left side and said that she was numb over both hips, had pins and needles going down her right leg, that her left hip was painful and tender and that weight bearing was not possible. She had no urinary symptoms and had normal voiding sensation. Her bowels had not been opened for 4 days, but until then had been regular. Her haemoglobin on admission was only 6·1 g/dl. She was examined in the right lateral position as nothing would induce her to lie on her back. The uterus could not be felt, but she appeared to have a large extra peritoneal mass in the left flank, the right flank could not be examined adequately. The spine, sacrum and right sacroiliac joint were not tender, but the left sacroiliac joint appeared to have undergone disruption and a finger could be inserted between the ala of the sacrum and the iliac bone. This area was extremely tender and appeared slightly swollen. Only minimal separation of the symphysis could be felt and this was non tender.

Haematological investigations were made to exclude clotting or haemolytic disorders. Blood was transfused and a pelvic X-ray and CT scan were performed. The X-ray (Fig. 1) showed asymmetry of the left side of the pelvis with widening of the left sacroiliac joint and some irregularity of the joint margins, but no bone resorption. The pelvic CT (Fig. 2) showed a large lobulated mass around the left sacroiliac joint extending posteriorly into the buttock, inferiorly into the pelvis and upwards into the abdomen. The margins of the sacroiliac joint appeared disrupted. Orthopaedic advice was taken about further treatment and external fixation was not advised.

An arteriogram to exclude an aneurysm or an A/V malformation was advised in view of the size of the suspected haematoma. An examination under anaesthesia was carried out at the same time as the arteriogram. A left sided abdominal mass was easily felt, extending retroperitoneally from the pelvis to the left hypochondrium. Vaginal examination showed that the left pelvic wall protruded further into the pelvic cavity than did the right, and the lower pole of the left sided mass reached the level of the cervix and had opened out the left broad ligament. The arteriogram showed no evidence of an aneurysm or an A/V

Correspondence: Mr Pratik N. Shah, Registrar, Obstetrics and Gynaecology, West London Hospital, Hammersmith Road, Hammersmith, London W6 7QJ.

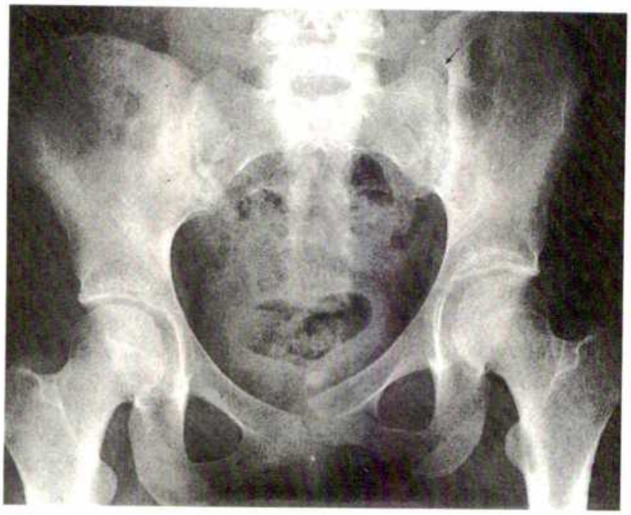


Fig. 1. Pelvic X-ray showing disruption of the left sacroiliac joint.

malformation suggesting that the suspected haematoma must have been venous in origin. Accordingly, it was decided to attempt a venogram, but this was abandoned when odourless pus was aspirated medial to the left femoral artery. A drainage catheter was inserted under CT guidance and drained over 500 ml of pus over the next 48 h before it fell out. A pure growth of pneumococcus was obtained and she was treated with benzyl penicillin. Cultures to exclude *Mycobacterium tuberculosis* were negative after 4 weeks.

She seemed to make some improvement over the next few days but then had an episode of haematemesis and malaena and in addition, the small swelling posteriorly over the left sacroiliac joint had become more pronounced and was now hot and tender. She was started on ranitidine and a large abscess which had tracked through the left sacrosciatic notch was drained. Gastroscopy at the same time revealed multiple small ulcers in the oesophagus and the prepyloric area. These were probably a result of excessive aspirin usage before admission.

She recovered quickly and on discharge was walking unaided without any pain. She was followed up 3 months later when she was symptom free and pelvic examination was entirely normal. The right sacroiliac joint felt normal and there was no tenderness.

Discussion

As far as we are aware this is the first report in the English literature of a retroperitoneal abscess following a normal delivery. It is postulated that in our patient disruption of the sacroiliac joint at delivery resulted in a retroperitoneal haematoma which became infected leading to a retroperitoneal abscess.

Diagnosis of a retroperitoneal abscess is often a diagnostic challenge but this is especially so in pregnancy where physiological relaxation of the sacroiliac joints can be symptomatic masking the diagnosis. It is often an insidious illness marked by diagnostic delay, inadequate drainage and considerable morbidity. Modern imaging techniques such as computed tomography and magnetic resonance imaging have been used successfully to aid the diagnosis and treatment of retroperitoneal abscesses (Gordon *et al.* 1987).

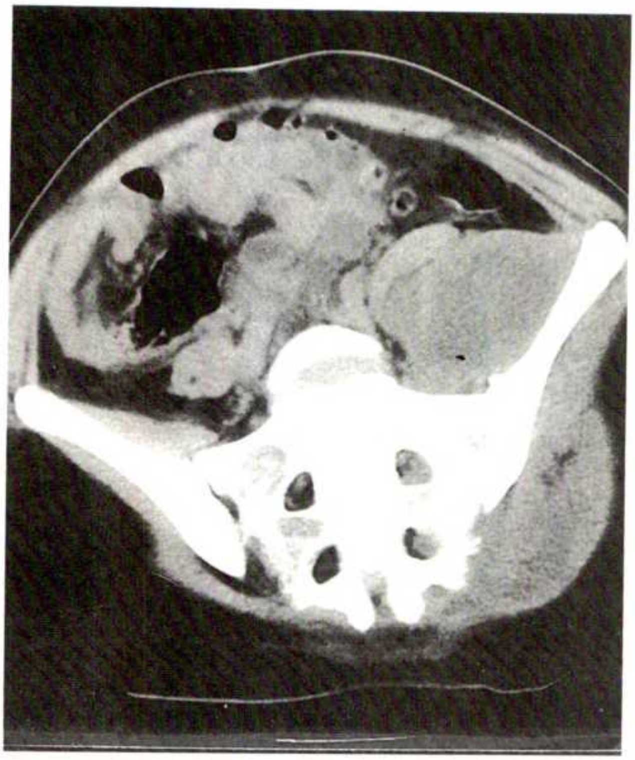


Fig. 2. CT scan of pelvis showing large left sided retroperitoneal mass.

Anatomic changes in the pelvis after uncomplicated vaginal delivery have been studied with the use of CT scans by Gargiola *et al.* (1989) who concluded that normal changes in the pelvis after an uncomplicated vaginal delivery included widening of the symphysis and sacroiliac joints. Interestingly he also noted gas in the joints and in one patient an asymptomatic muscle haematoma. The exact relevance of these findings to pelvic joint pain during or shortly after pregnancy is not clear.

References

Gargiola D. M., Tarver R. D., Gibson L., Rogers R. E. & Wass J. L. (1989) Anatomic changes in the pelvis after uncomplicated vaginal delivery; a CT study on 14 women. *A JR* **153,** 1239-1241.

Gordon D. H., Macchia R. J., Glanz S., Koser M. W. & Laungani G. B. (1987) Percutaneous management of retroperitoneal abscesses. *Urology* **30,** 299-306.

Received 15 July 1991
Accepted 4 September 1991

British Journal of Obstetrics and Gynaecology
February 1992, Vol. 99, pp. 162–163

Maternal death due to sickle cell chronic lung disease

A. VAN ENK
Gynecologist
G. VISSCHERS
Pulmonologist
W. JANSEN
Pathologist
L. W. STATIUS VAN EPS
Internist
Slotervaartziekenhuis, Louwesweg 6, 1066 EC Amsterdam

Case report

A 33-year-old woman with homozygous sickle cell anaemia was admitted in the 31st week of her fourth pregnancy for persistent dry cough, fetal growth retardation and a bad obstetric history. Her medical history included a bilateral total hip replacement for aseptic necrosis. She was admitted several times with painful bone and joint crises and once with the acute febrile chest syndrome. She had never been treated with exchange blood transfusions.

Examination after admission yielded the following results. Chest film: heart size just within normal limits, pulmonary trunk and hilar vessels slightly prominent; lung vessel pattern irregular and suggestive of widespread peripheral vascular obliteration. Lung function test showed a restrictive pattern (vital capacity 64% of predicted) without obstruction of airflow and a diminished CO transfer (K CO 61% of predicted); arterial blood gases showed hyperventilation and mild hypoxia (Po_2 71·2 mmHg, Pco_2 27·9 mmHg).

Further investigations were advised but refused by the patient. Because of intrauterine growth retardation it was decided to perform a caesarean section in the 36th week of pregnancy. Late in the afternoon of the fifth day of the 35th week the patient complained of a feeling of fulness in the upper abdomen, nausea and general malaise. She was slightly dyspnoeic but had no fever or pains. General physical examination did not reveal any particular abnormality but laboratory tests showed a rise in Hb, SGOT and SGPT from the previous day from 9·7 to 11·3 g/dl, from 53 to 70 and 19 to 23 U/l, respectively. The bilirubin values were normal.

A clear cause for her new symptoms could not be established. Early the following morning she collapsed, with acute dyspnoea and cyanosis. The Hb level was 7·2 g/dl. The central venous pressure was considerably raised. The electrocardiogram showed a pattern that could be associated either with extreme pulmonary hypertension or with anterior wall ischaemia. Cardiac ultrasound examination demonstrated a considerably enlarged right ventricle.

A preliminary diagnosis was made of pulmonary embolism accompanied by a haemolytic crisis, and she was treated accordingly. However, improvement did not occur. In the meantime the fetal heart rate pattern was suggestive of severe fetal distress. An emergency caesarean section was performed and a boy of 1800 g was born in poor condition. He recovered slowly but satisfactorily. His mother's condition however deteriorated rapidly and she died 8 h after surgery.

At postmortem examination the right atrium and ventricle were widely dilated. There was a small subendocardial myocardial infarct but no coronary arteriosclerosis. The pulmonary vessels were considerably enlarged. There was extensive arteriolar obliteration with subendothelial thickening and interstitial fibrosis (Figs. 1 and 2). Thromboemboli were not found and there were no signs of pulmonary infection or septicaemia.

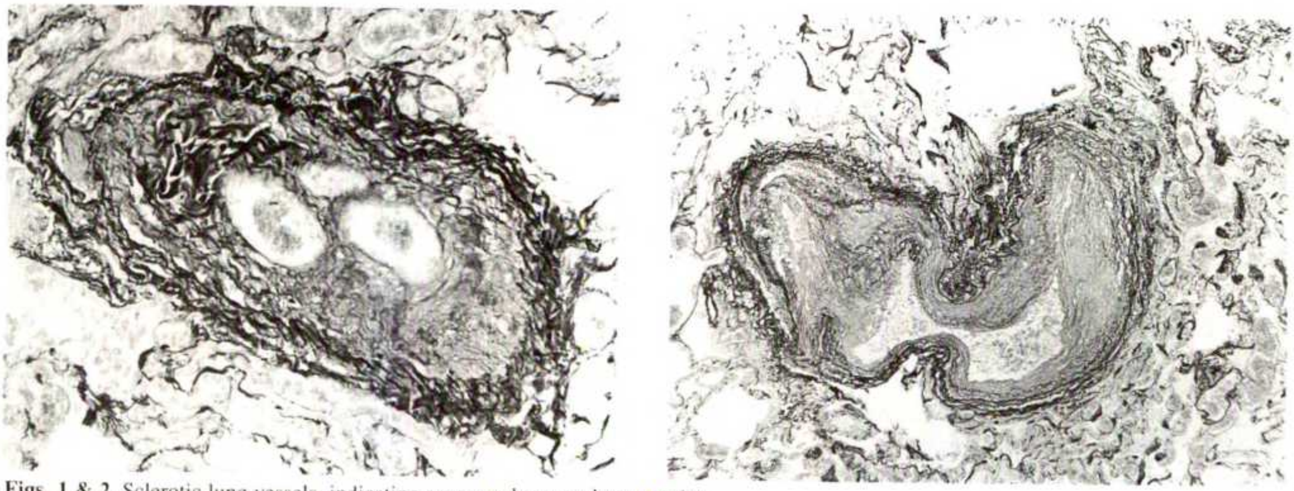
Discussion

The clinical findings and autopsy show that death was due to right heart failure subsequent to a small myocardial infarct in association with sickle cell chronic lung disease.

The latter is thought to develop in those with sickle cell disease because of chronic damage to the endothelium of the arterioli. The low O_2 pressure and the sluggish flow of blood in the pulmonary vessels consequent on sickling are assumed to be promoting factors (Powars *et al.* 1988). As a result, widespread obliteration of the arterioli takes place and interstitial fibrosis develops (Powars *et al.* 1988). This leads to decreased pulmonary function, pulmonary hypertension and cor pulmonale. The immediate cause of death in 50% of a series of 28 patients described by Powars *et al.* (1988) was subendocardial infarct without atherosclerosis.

Powars *et al.* (1988) could not find more than 28 published cases up to 1988 in spite of the disease having been described over 60 years ago. They added another 28 patients of whom half had died. Of these 25 had SS disease and all had very low Hb levels (as had the patient reported here). Early complaints of the patients in their series were cough and recurrent attacks of retrosternal pain. In a case-control analysis a significant association with adult aseptic bone necrosis and the sudden adult death syndrome was found. They suggest the latter being due to myocardial infarct—without coronary disease—which was present in all the patients who had a postmortem. Although until now no maternal deaths due to sickle cell chronic lung disease have been reported—which can be explained by its rarity—but pregnancy can be assumed to be associated with a strongly increased risk. Homozygous sickle

Correspondence: Dr A. van Enk.



Figs. 1 & 2. Sclerotic lung vessels, indicating severe pulmonary hypertension.

cell disease on its own is associated with a small risk of chronic lung disease (Powars *et al.* 1986). In combination with pulmonary hypertension, which has a high mortality in pregnancy (McCaffrey *et al.* 1964), the risk can be assumed to be high enough to justify advising a woman strongly against pregnancy.

Acknowledgments

We are indebted to Drs David Batchelor and J. Lindeman for their linguistic and expert radiologic and histo-pathologic help.

References

McCaffrey R. M. & Dunn L. J. (1964) Primary pulmonary hypertension in pregnancy. *Obstet Gynecol Surv* **19,** 567–571.

Powars D. R., Weidman J. A., Odom-Maryon T., Niland J. & Johnson C. (1988) Sickle cell chronic lung disease: Prior morbidity and the risk of pulmonary failure. *Medicine* **67,** 66–77.

Powars D. R., Sandhu M., Niland-Weiss, Johnson C., Bruce S. & Manning P. R. (1986) Pregnancy in sickle cell disease. *Obstet Gynecol* **67,** 217–228.

Received 12 March 1991
Accepted 24 September 1991

British Journal of Obstetrics and Gynaecology
February 1992, Vol. 99, pp. 163–166

Management of patients with severe hypertriglyceridaemia during pregnancy: report of two cases with familial lipoprotein lipase deficiency

G. F. WATTS
Lecturer
Department of Endocrinology and Chemical Pathology
K. MORTON
Lecturer
Department of Obstetrics and Gynaecology
P. JACKSON
Dietitian
Department of Endocrinology and Chemical Pathology
UMDS, St. Thomas' Hospital, London SE1 7EH
B. LEWIS
Emeritus Professor
University of London

Correspondence: Dr G. F. Watts, BSc DM MRCP.

Case reports

Patient 1

A 30-year-old midwife had experienced recurrent bouts of abdominal pain, occasionally precipitated by fatty meals, since childhood. Her parents were consanguineous. She presented to another hospital at 25 weeks gestation in her first pregnancy with severe abdominal pain, hypotension and lipaemic plasma. Acute pancreatitis was diagnosed (plasma amylase 1255 IU/l). The plasma concentrations of cholesterol and triglyceride were 16·0 and 50·0 mmol/l, respectively (normal upper limits 5·2 and 2·3 mmol/l, respectively). She was treated conservatively with intravenous crystalloids and nasogastric suction and she made a prompt recovery, but 5 days later she miscarried a small-for-gestational-age fetus (weight 1000 g). She was sterilized. In the following months she exhibited persistent hypertriglyceridaemia (about 25 mmol/l) despite taking a fat-modified diet and she was then referred to our lipid clinic. Lipoprotein ultracentrifugation of fasting plasma revealed excessive accumulation of chylomicrons with a modest elevation of very low density lipoproteins. There was no biochemical evidence of diabetes mellitus, hypothyroidism, liver disease or renal insufficiency; she denied taking alcohol, she was not overweight and an oral cholecystogram was normal. Twelve months post-partum lipoprotein lipase activity, measured in post-heparin (40 U/kg) plasma, was 0·2 μmol free fatty acids/ml/h (reference range 3·4–11·7); hepatic lipase activity and the level of apolipoprotein C-II (by isoelectric focusing of very low density lipoprotein) were normal. She began an isocaloric, 25 g fat diet (supplemented with medium-chain triglycerides) following which she has been free of abdominal pain for 15 years and her plasma triglyceride level has ranged from 10 to 15 mmol/l. Her younger brother was also found to have hyperchylomicronaemia due to lipoprotein lipase deficiency and he has responded well to dietary treatment.

Patient 2

A 22-year-old clerk had previously undergone appendectomy at the age of 6 years, after presenting with acute abdominal pain. Histological examination of the appendix was normal. Postoperatively she was found to have lipaemic plasma. The fasting plasma concentrations of cholesterol and triglyceride were 5·8 and 30·0 mmol/l, respectively; ultracentrifugation revealed excessive accumulation of chylomicron particles. Plasma post-heparin lipoprotein lipase activity was 0·3 μmol free fatty acids/ml/h, hepatic lipase activity and apolipoprotein C-II (in very low density lipoprotein) were both normal. The diagnosis of lipoprotein deficiency was made. All her relatives were normolipidaemic and there were no causes of secondary hypertriglyceridaemia. An isocaloric, 30 g fat diet was prescribed. As a teenager she suffered recurrent abdominal pain and she had three confirmed episodes of pancreatitis, all associated with dietary non-compliance, eruptive xanthomata, lipaemia retinalis and hypertriglyceridaemia (>50 mmol/l).

Table 1. Nutrient composition of low fat diets used to manage a patient with lipoprotein lipase deficiency during pregnancy (Patient 2), compared with the recommended dietary allowance for pregnant women (DHSS 1979)

Nutrient	30 g fat diet* (outpatient)	10 g fat diet* (inpatient)	Recommended dietary‡ allowance in pregnancy
Calories (kcal) (1 kcal = 4·12 kJ)	2070	1510	2400
Protein (g)	94·5	79	60
Fat (g)	27·5	11·5	—
Polyunsaturated fatty acids (g)	8·0	3·5	—
Carbohydrate (g)	385	288	—
Calcium (mg)	800	1100	1200
Iron (mg)	13·2	11·0	13
Zinc (mg)	12	10	—
Vitamin A (μg)	317†	360†	750
Vitamin D (μg)	1·5†	0·1†	10
Vitamin E (μg)	5·3	2·8	—
Thiamine (mg)	1·2	1·4	1·0
Riboflavin (mg)	1·6	2·3	1·6
Nicotinic acid (mg)	26	22	18
Folic acid (μg)	250	270	—
Vitamin C (mg)	75	115	60
Vitamin B_{12} (mg)	2·7	4·2	—
Vitamin B_6 (mg)	1·7	2·6	—

*Both diets were supplemented with iron and multivitamins.

†Supplements provided 1500 μg vitamin A and 12·5 μg vitamin D per day.

‡Published recommendations only given.

She attended the lipid clinic with a 6-week history of amenorrhea, a routine pregnancy test being positive; pregnancy was subsequently confirmed by ultrasonography. Because of her previous history she was kept under strict medical supervision. Although in the first trimester the plasma triglyceride concentration was kept below 15 mmol/l on an isocaloric, 30 g fat diet (Table 1), the concentration climbed sharply after 24 weeks gestation (Fig. 1). However, further restriction of calories and fat (Table 1) during two brief antenatal admissions to hospital maintained the plasma triglyceride concentration below 25 mmol/l (Fig. 1). Her weight increased from 50 kg before pregnancy to 57 kg at the end of the second trimester and remained stable at 58 kg during the third trimester. At all stages of the pregnancy, lipoprotein ultracentrifugation revealed that the hypertriglyceridaemia was due to accumulation of both very low density lipoproteins and chylomicron particles. All her diets were supplemented with fat-soluble vitamins, but she could not tolerate medium-chain triglycerides. She remained asymptomatic. Labour was induced at 40 weeks gestation and she gave birth to a healthy male infant, birthweight 3·0 kg with a cord plasma triglyceride concentration of 0·14 mmol/l. After delivery her plasma triglyceride concentration fell rapidly to <10 mmol/l (Fig. 1), and it remained at 10–20 mmol/l on a 30 g fat diet. During the

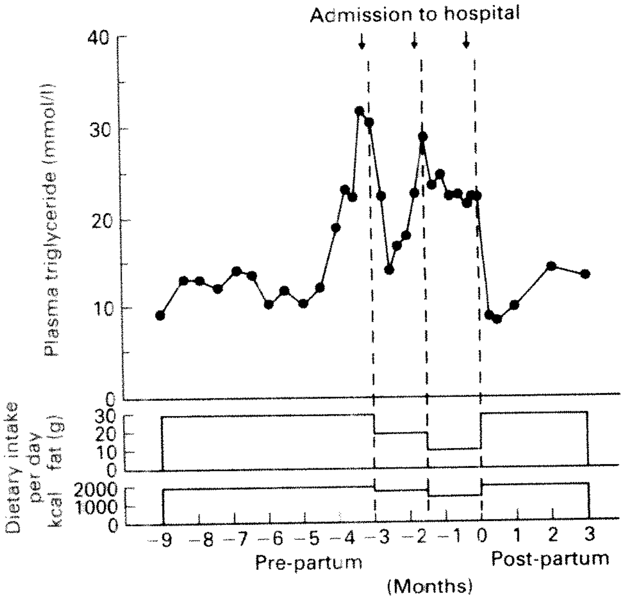


Fig. 1. Plasma concentration of triglyceride and dietary intake during and after pregnancy in a young woman with familial lipoprotein lipase deficiency. 1 kcal = 4·12 kJ.

course of the next 5 years she had no further attacks of acute pancreatitis or abdominal pain and she had a second successful pregnancy in which a protocol similar to the above was followed.

Discussion

Lipoprotein lipase is a lipolytic enzyme which is bound to the luminal surface of capillary endothelial cells and plays a pivotal role in the catabolism of triglyceride-rich lipoproteins (Eckel 1989). Genetic deficiencies of lipoprotein lipase or of its co-factor, apolipoprotein C-II, are rare but they may lead to severe chylomicronaemia, eruptive xanthomata and acute pancreatitis in affected subjects (Havel *et al.* 1980; Nikkila 1983). The risk of premature cardiovascular disease is not increased. Lipoprotein lipase deficiency follows an autosomal recessive pattern of inheritance (Eckel 1989).

The rise in plasma oestrogen levels during pregnancy increases hepatic production of triglyceride-rich very low density lipoproteins (Kissebah & Schectman 1987). This may be compounded by increased adipose tissue lipolysis due to human placental lactogen (Williams & Coltart 1978). Accordingly, in normal subjects, pregnancy is commonly associated with a modest elevation in plasma triglyceride level (Warth *et al.* 1975). Women with lipoprotein lipase deficiency, however, have a markedly reduce lipolytic capacity and during the last two trimesters they may develop pronounced hypertriglyceridaemia owing to accumulation of very low density lipoproteins and chylomicrons (Havel *et al.* 1980).

Patient no. 1 shows that if lipoprotein lipase deficiency is undiagnosed or inadequately managed, acute pancreatitis, a common complication of chylomicronaemia (Cameron *et al.* 1972), may ensue with catastrophic consequences in pregnancy. Patient no. 2 demonstrates that a favourable outcome may be achieved by recognition of the disorder before conception (or early in pregnancy), close monitoring of the plasma triglyceride concentration and graded restriction of dietary energy and fat intake. There have only been two previous reports of pregnancy in patients with confirmed familial lipoprotein lipase deficiency (Havel *et al.* 1980; Steiner *et al.* 1985). Both women developed severe chylomicronaemia and acute pancreatitis in the last trimester, in one despite the elimination of fat from her diet (Havel *et al.* 1980). A patient described by Adlersberg *et al.* (1959) might have had familial lipoprotein lipase deficiency, but this was not confirmed biochemically; following covert presentation with acute pancreatitis her plasma triglyceride levels were controlled in hospital with fat restriction. That pregnancy exacerbates hypertriglyceridaemia and increases the risk of acute pancreatitis in familial hyperlipidaemias other than lipoprotein lipase deficiency has been reported previously (Millen *et al.* 1956; Glueck *et al.* 1980). These patients have also been treated successfully with diet alone. Some authors have suggested the use of parenteral nutrition (Weinberg *et al.* 1982; Sanderson *et al.* 1991), but we feel that this may be unwarranted provided care is taken to reduce dietary fat and energy intake sufficiently (Patient 2).

To recognise lipoprotein lipase deficiency and other primary hypertriglyceridaemias (Glueck *et al.* 1980), visual inspection of a fasting plasma sample for lactescence should be undertaken routinely in early pregnancy. If indicated this should be followed by measurement of fasting plasma lipids. Familial lipoprotein lipase deficiency should be considered in anyone with a suspicious history of unexplained, recurrent abdominal pain in childhood, exanthematous-like rashes on extenor surfaces and parental consanguinity (Havel *et al.* 1980; Nikkila 1983). Before pregnancy lipoprotein fractionation will reveal gross accumulation of chylomicrons with a modest increase in very low density lipoproteins. During pregnancy, however, these lipoproteins will be present in plasma in equimolar amounts (Havel *et al.* 1980). The definitive diagnosis relies on an enzyme assay either in a post-heparin blood sample or in an adipose tissue biopsy (Brunzell *et al.* 1980) and exclusion of deficiency of apolipoprotein C-II (Breckenridge *et al.* 1978) or the presence of an inhibitor of lipoprotein lipase (Brunzell *et al.* 1983).

In pregnancy, referral to, and joint management with, a physician with a specialist interest in lipid disorders is recommended. Dietary treatment should aim to keep the plasma triglyceride level below 10–15 mmol/l (Havel *et al.* 1980; Nikkila 1983). A target level of 10 mmol/l may be achieved in the first trimester with a diet containing 25–30 g fat, with attention to ensuring an adequate supply of essential fatty acids, vitamins, and micro-nutrients (Table 1). Plasma triglyceride response should ideally be monitored using both fasting and post-prandial samples. Fat and energy intake may have to be reduced further later in pregnancy, restriction of carbohydrates being important to avoid exacerbating endogenous hypertrigyceridaemia (Ahrens *et al.* 1961). Because low fat diets are difficult and monotonous to follow frequent dietetic monitoring, not only to confirm compliance, but also to assess nutritional adequacy and weight gain is necessary (DHSS 1979). Nutritional supplementation with fat-soluble vitamins will be required. Diets containing <20 g fat per day are also likely to be low in essential fatty acids, but clinical deficiency is only seen when these acids provide less than 1–2% of total dietary energy (Passmore & Eastwood 1986). Medium chain triglycerides which channel directly into the portal circulation and are not hydrolysed by lipoprotein lipase should be considered for cooking purposes, but palatability and cost may limit their use. There is no place for the use of anti-lipaemic medication and, with due attention to the recommendations given in the present report, invasive treatments, such as parenteral nutrition and plasma exchange, will not be required (Weinberg *et al.* 1982; Sanderson *et al.* 1991; Yamauchi *et al.* 1986).

Women with lipoprotein lipase deficiency should not breast feed since absence of the enzyme in mammary tissue results in nutritionally deficient milk (Steiner *et al.* 1985). Moreover, oestrogen containing contraceptives should not be prescribed since they exacerbate hypertriglyceridaemia and increase the risk of pancreatitis (Davidoff *et al.* 1973; Stuyt *et al.* 1986).

Acknowledgment

We thank Mr W. Jefferson for typing the manuscript.

References

Adlersberg D., Feldman E. B., Kaplan S. & Wang C. I. (1959) Hyperlipidaemia and pancreatitis, hypercholesterolaemia and coronary heart disease complicating pregnancy. *Am J Obstet Gynecol* **78**, 851-859.

Ahrens E. H., Hirsch J., Oette K., Farquhar J. W. & Stein Y. (1961) Carbohydrate-induced and fat-induce lipaemia. *Trans Assoc Am Physicians* **74,** 134-146.

Brenkenridge W. C., Little J. & Steiner G. (1978) Hypertriglyceridaemia associated with apolipoprotein C-II deficiency. *N Engl J Med* **298,** 1265-1273.

Brunzell J. D., Chait A., Nikkila E. A., Ehnholm C., Huttunen J. K. & Steiner G. (1980) Heterogeneity of primary lipoprotein lipase deficiency. *Metabolism* **29,** 624-629.

Brunzell J. D., Miller N. E., Alaupovic S. *et al.* (1983) Familial chylomicronaemia due to a circulating inhibitor of lipoprotein lipase activity. *J Lipid Res* **12,** 12-19.

Cameron J. L., Capuzzi D. M., Zuidema G. D. & Margolis S. (1972) Acute pancreatitis with hyperlipidaemia: incidence of lipid abnormalities in acute pancreatitis. *Ann Surg* **177,** 483-489.

Davidoff F., Tishler S. & Rosoff C. (1973) Marked hyperlipidaemia and pancreatitis associated with oral contraception use. *N Engl J Med* **289,** 552-555.

DHSS (1979) Recommended daily amounts of food energy and nutrients for groups of people in the UK. *Report on Health and Social Subjects* **15,** HMSO, London.

Eckel R. H. (1989) Lipoprotein lipase. *N Engl J Med* **320,** 1060-1068.

Glueck C. J., Christopher C, Mishkel M. A., Tsang R. C. & Mellies M. J. (1980) Pancreatitis, familial hypertriglyceridaemia and pregnancy. *Am J Obstet Gynecol* **136,** 775-761.

Havel R. J., Goldstein J. L. & Brown M. S. (1980) Lipoproteins and lipid transport. In *Metabolic Control and Disease* (Bondy P. K. & Rosenberg L. E., eds), Saunders, Philadelphia, pp. 415-422.

Kissebah A. H. & Schectman G. (1987) Hormones and lipoprotein metabolism. *Baillieres Clin Endocrinol Metab* **3,** 699-725

Millen R. S., Russ E. M., Eder H. A. & Barr D. P. (1956) Pregnancy complicated by hyperlipidaemia. *Am J Obstet Gynecol* **71,** 326-330.

Nikkila E. A. (1983) Familial lipoprotein lipase deficiency and related disorders of chylomicron metabolism. In *The Metabolic Basis of Inherited Disease* 5th edn, (Stanbury J. B., Wyngaarden J. B., Fredrickson D., Goldstein J. L. & Brown M. S., eds), McGraw-Hill Book Co., New York, pp. 622-642.

Passmore R. & Eastwood M. A. (1986) *Human Nutrition and Dietetics.* 8th edn. Churchill Livingstone, Edinburgh, p. 67.

Sanderson S. L., Iverius P.-H. & Wilson D. E. (1991) Successful hyperlipemic pregnancy. *JAMA* **265,** 1858-1860.

Steiner G., Myher J. J. & Kuksis A. (1985) Milk and plasma lipid composition in a lactating patient with type I hyperlipoproteinaemia. *Am J Clin Nutr* **41,** 121-128.

Stuyt P. M., Demacker P. N. M. & Stalenhoef A. F. M. (1986) Pancreatitis induced by oestrogen in a patient with type I hyperlipoproteinaemia. *Br Med J* **293,** 734.

Warth M. R., Arky R. A. & Knopp R. H. (1975) Lipid metabolism in pregnancy III. Altered lipid composition in intermediate, very low, low and high density lipoprotein fractions. *J Endocrinol Metab* **41,** 649-655.

Weinberg R. B., Sitrin M. D., Adkins G. M. & Lin C. (1982) Treatment of hyperlipidaemic pancreatitis in pregnancy with total parenteral nutrition. *Gastroenterology* **83,** 1300-1305.

Williams C. & Coltart T. M. (1978) Adipose tissue metabolism in pregnancy. *Br J Obstet Gynaecol* **85,** 43-46.

Yamauchi H., Sunamara M., Takeda K., Suzuki T., Itoh K. & Miyagawa K. (1986) Hyperlipidaemia and pregnancy-associated pancreatitis with reference to plasma exchange as a therapeutic intervention. *Tohoku J Exp Med* **148,** 197-205.

Received 17 July 1991
Accepted 14 October 1991

British Journal of Obstetrics and Gynaecology
February 1992, Vol. 99, pp. 167–168

SHORT COMMUNICATION

ST-waveform analysis of the fetal electrocardiogram could reduce fetal blood sampling

R. B. JOHANSON
C. RICE
A. SHOKR
M. DOYLE
R. CHENOY
P. M. S. O'BRIEN

Keele University Academic Department of Obstetrics and Gynaecology, North Staffordshire Maternity Hospital, Hilton Road, Stoke-on-Trent ST4 6SD

With the need to improve fetal surveillance in labour, interest has focused on further analysis of the electrocardiogram (ECG) and fetal acid-base status. There is convincing experimental evidence that hypoxia results in changes in the ST-wave form of the ECG with ST segment elevation and high T waves, which can be quantified by the T/QRS ratio (Greene 1987). Clinical studies have also demonstrated the appearance of these changes in the scalp ECG during labour, particularly in cases with metabolic acidosis (Arulkumaran *et al.* 1989). In that study a T/QRS ratio identified with 99·3% accuracy a fetus with normal buffering capacity in the cord blood. We wished to study the immediate relation between the T/QRS ratio and acid-base changes noted at the time of fetal blood sampling (FBS) for fetal distress and to assess the possibility of reducing fetal blood sampling by utilizing in its place ST-wave form analysis.

Methods

Whenever the CTG trace, using a single-helix electrode, suggested fetal distress in labour the STAN-recorder (Cinventa-AB, Sweden) was connected and a scalp fetal blood sample was obtained. Full analysis of the acid-base status (pH, $P\text{CO}_2$ standard HCO_3 and base excess) of a 50 μl sample was undertaken using a Corning blood gas analyser. The STAN-recorder presents the fetal heart rate, uterine activity, T/QRS ratios and real-time averages of ECG complexes on a paper print-out as described previously by Lilja *et al* (1988) and Arulkumaran *et al.* (1990). The individual T/QRS ratio at the time of the FBS was noted. In addition an average of the closest five T/QRS ratios obtained, from plotted ECG complexes with optimal signal quality.

Results

In the study a total of 88 scalp blood samples were obtained from 52 fetuses. The quality of the tracings presented by the STAN monitor were such that immediate ST-waveform assessment was possible in all but three of the instances (in two there was evidence of 50Hz electrical interference). In the third the signal quality was poor, the first T/QRS ratio that could be read occurred 20 min after the FBS was obtained. The range of pH was 6·95–7·46. The range in base excess was 7·5 to 16·0 mmol/l. Although nine babies were acidotic (pH<7·2) by traditional criteria (Bretscher & Saling 1967) in only three of these was there evidence of a significant metabolic component (with a base excess >12 mmol/l (Sykes *et al.* (1982)). None had an ST-segment depression or T-wave inversion. The three babies with metabolic acidosis had the following pH and base excess results: (1) 7·05 and 15·2; (2) 7·17 and 15·0 and (3) 6·95 and 16.

In all but 10 of the instances the average was based on five T/QRS ratios. In these 10 it was based on an average of between two and four ratios.

The average T/QRS ratio was <0·25 in all the instances except in two of the three acidotic fetuses where it was 0·27 (2) and 0·32 (3); in the third acidotic fetus (1) the trace had a poor signal quality. A single T/QRS reading on this trace 20 min after the FBS was normal.

Discussion

An ECG average T/QRS ratio >0·25 was observed in two fetuses with scalp metabolic acidosis. The STAN-recording of the only other fetus with this degree of acidosis in the study unfortunately did not provide data at the time of FBS. The detection rate in this study was therefore 66% with one 'failure' of the method.

However, in a parallel clinical situation (with 88 instances where an FBS was indicated), 83 of the STAN-recordings would have correctly reassured the obstetrician, two would have resulted in the detection of fetuses at risk from metabolic acidosis and three (because of the poor signal quality of the STAN-record) would have required an FBS (which would have picked up the other fetus with significant acidosis). Fetal blood sampling may be uncomfortable for the mother, may leave marks on the scalp and may be implicated in unnecessary delays before delivery. It is possible that the STAN-monitor may provide a non-invasive method for obtaining information about the fetus compromised by acidosis.

Conclusion

We have shown that fetal ECG ST-waveform analysis with the STAN monitor can be undertaken in situations which clinically indicate an FBS. The data indicate that the T/QRS ratio may provide independent information from heart rate and that this

Correspondence: R. B. Johanson.

information could be most useful in separating physiological from pathological CTG traces. Whether the STAN-monitor will eventually replace conventional monitoring and fetal blood sampling in routine obstetric practice will depend upon the results of other studies at present underway.

References

Arulkumaran S., Lilja H., Lindecrantz K., Ratnam S. S., Thavarasah A. S. & Rosen K. G. (1990) Fetal ECG waveform analysis should improve fetal surveillance in labour. *J Perinat Med* **18,** 13-21.

Bretscher J. & Saling E. (1967) pH values in the human fetus during labour. *Am J Obstet Gynecol* **97,** 906-911.

Green K. R. (1987) The ECG waveform. *Baillieres Clin Obstet Gynaecol* **1,** 131-155.

Lilja H., Arulkumaran S., Lindecrantz K., Ratnam S. S., Rosen K. G. (1988) Fetal ECG during labour: a presentation of a microprocessor system. *J Biomed Eng* **10,** 348-350.

Sykes G. S., Johnson P., Ashworth F., Molloy P. M., Gu W., Stirratt G. M. & Turnbull A. C. (1982) Do Apgar scores indicate asphyxia? *Lancet* **i,** 494-496.

British Journal of Obstetrics and Gynaecology
February 1992, Vol. 99, pp. 169–172

CORRESPONDENCE

Is GIFT (gamete intrafallopian transfer) the best treatment for unexplained infertility?

Dear Sir,
The report of Murdoch *et al.* (1991) comparing GIFT with no treatment among 76 women with unexplained infertility was a thoughtful and well-analysed study. During 894 months of observation without treatment the average fecundability was 2·1% compared with 14% after 99 cycles of GIFT. Although GIFT seemed seven times better than no treatment, the authors were careful not to infer efficacy from the results of this comparison. Their caution is justified, because the different lengths of follow-up (a mean of 1·7 cycles of GIFT compared with 12·2 months of observation) introduce an unexpected bias that is related to better fecundability in the earlier months of observation.

When the follow-up of a group of infertile couples is analysed, those who are more likely to get pregnant will conceive early in the observation period. Unless new couples are added, the remainder will have fewer pregnancies during the later months of observation. Thus, selecting couples according to their length of follow-up can affect the observed fecundability and the cumulative pregnancy rate.

The cumulative pregnancy rates for livebirths among 340 untreated couples with unexplained infertility illustrate this point. Other details on these couples, some of whom were followed for 48 months, have been reported (Collins & Rowe, 1989). The fecundability was higher during the first 6 months compared with later months (Fig. 1). When the original 340 patients were divided into two groups (67 followed ≤3 months and 273 followed >3 months) the apparent fecundability in the group with shorter follow-up was very high, and the resulting cumulative pregnancy rate was similar to that seen with the GIFT cycles.

Based on this knowledge, an interesting comparison can be made from the data of Murdoch *et al.* There were 14 (26%) pregnancies among 53 couples who started GIFT cycles, and 5 (17%) among 30 couples who were followed without treatment for ≤3 months. This comparison gives an odds ratio of 1·79 with 95% confidence interval 0·58 to 5·58 which is not statistically significant.

This is not to suggest that control groups should be manipulated in this way, but that bias exists even when the baseline characteristics of groups are comparable, as in the study of Murdoch *et al.* The evidence needed to demonstrate the effectiveness of infertility treatments will have to come from randomized clinical trials. If GIFT is seven times better, the question could be tested in a group of about 80 couples, half of whom receive two cycles of GIFT while the other half wait without treatment for 2 months. Such a design avoids the pitfall of randomization by cycle and does not delay unduly the desired treatment for those allocated to serve as controls.

The report of Murdoch *et al.* is valuable in that it provides the information needed for the design of further trials. Probably GIFT is an

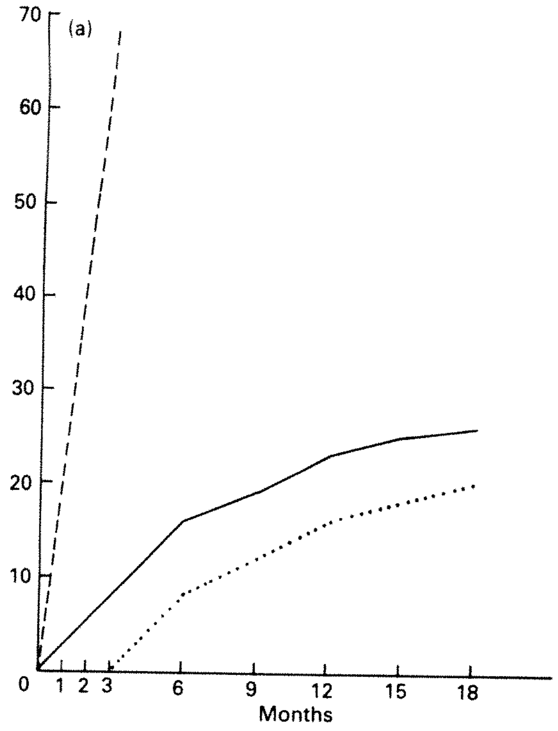


Fig. 1(a). Cumulative pregnancy rates among 340 untreated couples with unexplained infertility (———); 67 of the same couples followed ≤3 months (---------); the remaining 273 couples, followed more than 3 months (············).

Both life tables are terminated at 18 months.

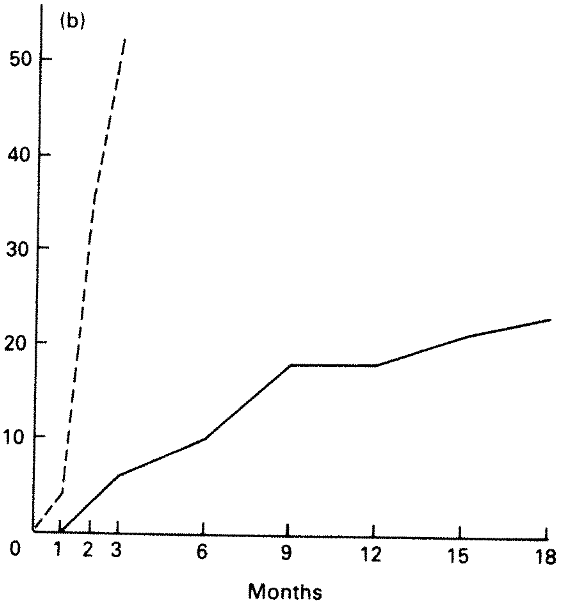


Fig. 1(b). Murdoch *et al.* (1991). 51 couples with at least 1 completed cycle of GIFT (---------); 76 couples observed without treatment (———).

effective treatment; certainly the world is not waiting for proof of that. Nevertheless, it is not too late for well-designed studies.

John Collins
Professor and Chairman
Department of Obstetrics & Gynecology

Murray Enkin
Professor Emeritus
Departments of Obstetrics & Gynecology
Clinical Epidemiology & Biostatistics
McMaster University
Hamilton
Ontario, Canada L8N3Z5

References

Collins J. A. & Rowe T. C. (1989) Age of the female partner is a prognostic factor in prolonged unexplained infertility: a multicenter study. *Fert Steril* **52**, 15–20.

Murdoch A. P., Harris M., Mahroo M., Williams M. & Dunlop W. (1991). Is GIFT (gamete intrafallopian transfer) the best treatment for unexplained infertility? *Br J Obstet Gynaecol* **98**, 643–647.

The place of oophorectomy at vaginal hysterectomy

Dear Sir,

Dr Sheth (1991) should be complimented for producing the largest ever series of bilateral oophorectomy at the time of vaginal hysterectomy. It is clear from his results that factors such as obesity, nulliparity, reduced pelvic space and enlargement of the uterus affect adversely the ability to remove the ovaries whereas, provided there was third degree descent of the uterus, it was always possible to remove the ovaries. It appears therefore that the single most important factor leading to successful vaginal oophorectomy is a major degree of uterine descent. Although not mentioned in Dr Sheth's paper, it would be of interest to know what proportion of the 64 patients with third degree descent had unfavourable factors and also what proportion of patients with first and second degree uterine descent had successful vaginal oophorectomy.

However, if surgical oophorectomy is not possible there is an alternative, namely to destroy the ovaries with electrocoagulation. This technique is practised in some of the district hospitals in India, Palanpur General Hospital being one of them. Although the work has not yet been published this procedure does not appear to be associated with significant morbidity provided the technique is carried out with care. The ovaries are pulled into or near the operative field by picking them up with forceps. After confirming that the ovaries are macroscopically normal, a biopsy is taken following which they are destroyed by bipolar electrocoagulation. Although one might expect haemorrhage to be a problem, it is only encountered occasionally. Destruction of the ovaries by electrocoagulation is a procedure which can be carried out with ease and should be considered in those in whom the ovaries cannot be removed surgically.

K. Dave
Department of Obstetrics & Gynaecology
The Birmingham & Midland Hospital for Women
Showell Green Lane
Sparkhill
Birmingham B11 4HL

Reference

Sheth S. S. (1991) The place of oophorectomy at vaginal hysterectomy. *B J Obstet Gynaecol* **98**, 662–666.

Author's reply

Dear Sir,

Mr Dave suggests that a major degree of uterine descent is a major factor allowing vaginal oophorectomy. In fact of 64 patients with third degree descent, 24 had unfavourable factors such as obesity, nulliparity or an enlarged uterus, but oophorectomy at vaginal hysterectomy was achieved in every case. There is no doubt that marked descent makes the ovaries more accessible. However, the single most important factor is to begin the learning process with easy cases and to progress in stages to oophorectomy when there is little descent.

In 428 patients with first and second degree uterine descent, vaginal oophorectomy was possible in 413 (96%).

It was interesting to note that direct ablation of ovary at vaginal hysterectomy can be performed safely using a bipolar cautery.

Shirish S. Sheth
Department of Obstetrics & Gynaecology
King Edward Memorial Hospital & Sheth
G.S. Medical College
Parel
Bombay 400 012
India

The surgical management of vaginal vault prolapse

Dear Sir,

The value of sacrocolpopexy is highlighted by Creighton & Stanton (1991). The technique may be adapted for surgery of uterine prolapse with congenital urological abnormalities such as ectopia vesicae, so maintaining sexual and reproductive functions. Three such hysterosacrocolpopexies, using a Goretex graft, have been performed with good results. The graft is wrapped around the uterus, passed through peritoneal tunnels in the broad ligaments and sutured to the sacral periosteum.

Sacrocolpopexy has a role in vaginal vault prolapse following major pelvic surgery for cancer even when this has been followed by radiotherapy. Six procedures have been performed, five after cancer surgery, followed by radiotherapy in two cases. We would agree with Creighton & Stanton (1991) that the risk of infection is real, as our only complication was of necrotizing fasciitis of the anterior abdominal wall and omental gangrene in a woman who had previously had an anterior exenteration for carcinoma of the bladder.

A. G. Farkas
Registrar in Gynaecology
John H. Shepherd
Consultant Gynaecological Surgeon & Oncologist
St Bartholomew's Hospital
West Smithfield
London EC1A 7BE

Dear Sir,

I was interested to note that Creighton & Stanton (1991) preferred the colposacropexy procedure to the abdomino-vaginal operation for vault prolapse There is, however, a small chance of 'mesh rejection' and colonic distortion or adhesions.

I use a modification of the Shirodkar sling operation wherein a 3 mm wide Mersilene tape is used to fix the vault to the first sacral vertebra. The uterosacral ligaments are fixed to the mid portion of the tape and both limbs are withdrawn retroperitoneally over the pelvic brim with a large aneurysm needle which is threaded from the sacral vertebra to the junction of the uterosacral ligaments. This is done on the right of the pelvis to avoid colonic compression or distortion. The sling is then pulled to the desired height and fixed to the anterior longitudinal ligament. The chance of 'rejection' is minimal since the amount of foreign material used is less. I have achieved satisfactory results in the seven women with vault prolapse and 18 with uterocervical prolapse treated so far.

Ajay Rane

Royal Liverpool University Hospital
Prescot Street
Liverpool L7 8XP

References

Creighton S. M. & Stanton S. L. (1991) The surgical management of vaginal vault prolapse. *Br J Obstet Gynaecol* **98**, 1150–1154.

A review of 80 endometrial resections for menorrhagia

Dear Sir,

Pyper & Haeri (1991) have put forward some important practical points on which to develop a safe and effective technique for trans-cervical endometrial resection (TCRE), albeit based on the outcome of a relatively small number of patients. As with any new procedure, patient safety must be of prime importance, a consideration easily overlooked in the attempt to achieve excellence.

Ideally trans-cervical endometrial resection should be undertaken without any hormonal preparation, between the 5th and 8th day of the cycle. It matters not if the uterus is still bleeding, since the blood and clot may be flushed out easily during the preliminary hysteroscopic assessment (which incidentally makes prior hysteroscopy unnecessary). The point is that the untreated endometrium, from which diagnostic histology may be obtained, will be thin at that stage of the cycle, often comparable to a down-regulated patient. Furthermore there will be substantially less intraoperative bleeding, especially at day 5. For this to work in practice, women need to be admitted on a week to week basis having telephoned the admissions secretary on day 1 of the period to check there is an available bed. One appreciates that this degree of flexibility is not always easy to achieve, but if it can, the system works well.

Fluid overload is always a worry, so Pyper & Haeri are absolutely right to emphasize the importance of observing strictly input/output volumes. If glycine is infused under pressure, some form of pressure monitoring is mandatory. Alternatively one can use gravity inflow of up to 100 cm glycine and regulate the uterine cavity distension by means of the suction outflow tap. In this way at Queen Charlotte's and Chelsea Hospital there have been no cases of clinically detectable fluid overload in 300 consecutive patients undergoing endometrial resection, nor has an operation needed to be abandoned because of excessive glycine absorption, the average figure for which is in the region of 0·25 litre.

One further point of practical consideration is that of using Cervagem (gemeprost 1 mg) pessaries preoperatively for nulliparous women and women who have been delivered only by caesarean section. It is a clinical impression that 1 mg gemeprost inserted 2 h before resection markedly softens the cervix so making dilatation to Hegar 9 or 10 very easy. This in turn allows for free movement of the resectoscope so reducing the risk of perforation and/or other trauma.

Tim Coltart

Queen Charlotte's and Chelsea Hospital
Goldhawk Road
London W6 0XG

References

Pyper R. J. D. & Haeri A. D. (1991) A review of 80 endometrial resections for menorrhagia. *Br J Obstet Gynaecol* **98**, 1049-1054.

Human immunodeficiency virus type 1 (HIV-1) seroconversion during pregnancy does not increase the risk of perinatal transmission

Dear Sir,

I am concerned about the paper by Tovo *et al* (1991). The authors have recorded ten women who seroconverted during pregnancy, the data are important and worth publishing, but the presentation is completely misleading. Increased viral load has been observed during primary HIV infection in homosexual men (Clark *et al* 1991) and it has been assumed that infectivity will be higher before neutralizing antibodies are produced (Pizzo & Butler 1991). Critical current interest in vertical transmission surrounds the possible protective effect of maternal antibodies to the external envelope glycoprotein gp 120, especially epitopes in the hypervariable V3 region (Rossi *et al* 1989; Goedert *et al* 1989; Devash *et al* 1990). This model is supportive of the concept that absence of antibody in early infection will result in high risk of transmission. The model is admittedly of uncertain validity at present because several authors have been unable to confirm the results (Parekh *et al*. 1991) and there are the theoretical objections that many patients carry virus variants which are not neutralized by their own sera (Albert *et al* 1990) and neutralizing antibodies would have a limited role if transmission occurs by the transfer of infected cells.

The issue is thus a complicated one (Mofenson & Burns 1991). Confirmatory clinical evidence of the increased transmission risk of early infection in pregnancy is limited. A national Swiss study (Rudin *et al*. 1991) found that two of four infants born to mothers who seroconverted during pregnancy developed severe symptoms of HIV infection at 1 and 3 months of age. Van de Perre *et al* (1991) identified 16 women in Rwanda who seroconverted after delivery and found nine of the infants (56%) became infected as judged by polymerase chain reaction, Western blotting, or both, before 18 months. It was judged that five, presumably a very high proportion of those exposed to risk, may have acquired HIV infection during late gestation or delivery (Pizzo & Butler 1991). In our total Edinburgh population, where seroconversion dates are generally known, vertical transmission is highly significantly more common in women who give birth within 1 year of seroconversion (Hague *et al* 1991).

Thus there are great uncertainties at present, but there is a little theoretical background and some preliminary experimental evidence to support the current belief that the higher viral load and lack of neutralizing antibody resulting from primary infection during pregnancy may predispose to a higher risk of vertical transmission. In contradicting current belief, the paper by Tovo *et al* (1991) does not explain what population was sampled, why only paediatric departments were involved in selecting the women, and whether the sample of seroconverters was known to be complete. There is no statistical presentation of the data. However, the finding of two infected babies out of ten (20%) has a 95% confidence interval extending to 56%. Compared with the large methodologically acceptable European Collaborative Study (1991) which found an overall transmission rate of 12·9%, the data are compatible with the view that vertical transmission is increased in such pregnancies. The authors are completely unjustified in their title 'HIV-1 seroconversion during pregnancy does not increase the risk of perinatal transmission' and in their statement 'these data strongly suggest that the risk of vertical HIV-1 transmission during primary infection is comparable to, *or at least not higher than*, that observed in chronic infection' (my italics)

F. D. Johnstone

Senior Lecturer
Department of Obstetrics & Gynaecology
Centre for Reproductive Biology
The University of Edinburgh
37 Chalmers Street
Edinburgh EH3 9EW

References

Albert J., Abrahamsson N., Nagy Y. *et al.* (1990) Rapid development of isolate-specific neutralizing antibodies after primary HIV-1 infection and consequent emergence of virus variants which resist neutralization by antologous sera. *AIDS* **4,** 107–112.

Clark S. J., Saag M. S., Decker W. D., *et al.* (1991) High titers of cytopathic virus in plasma of patients with symptomatic primary HIV-1 infection. *N Engl J Med* **324,** 954–960.

Devash Y., Calvelli T. A., Wood D. G., Reagan K. J. & Rubinstein A. (1990) Vertical transmission of human immunodeficiency virus is correlated with the absence of high-affinity/avidity maternal antibodies to the gp120 principal neutralizing domain. *Proc Natl Acad Sci USA* **87,** 3445–3447.

European Collaborative Study (1991) Children born to women with HIV-1 infection: natural history and risk of transmission. *Lancet* **337,** 253–260.

Goedert J. J., Mendez H., Drummond J. E., *et al.* (1989) Mother-to-infant transmission of human immunodeficiency virus type 1: association with prematurity or low anti-gp120. *Lancet* **ii,** 1351–1354.

Hague R. A., Mok J. Y. Q., MacCallum L., *et al.* (1991) Do maternal factors influence the risk of vertical transmission of HIV? VII International Conference on AIDS, Florence, June 1991. Abstract WC3237.

Mofenson L. M. & Burns D. N. (1991) Passive immunization to prevent mother-infant transmission of human immunodeficiency virus: current issues and future directions. *Pediatr Infect Dis J* **10,** 456–462.

Parekh B. S., Shaffer N., Pau C.-P., *et al.* (1991) Lack of correlation between maternal antibodies to V3 loop peptides of gp120 and perinatal transmission. *AIDS* **5,** 1179–1184.

Rizzo P. A. & Butler K. M. (1991) In the vertical transmission of HIV, timing may be everything. *N Engl J Med* **325,** 652–654.

Rossi P., Moschese V., Broliden P. A., *et al.* (1989) Presence of maternal antibodies to human immunodeficiency virus 1 envelope glycoprotein gp120 epitopes correlates with the uninfected status of children born to seropositive mothers. *Proc Natl Acad Sci USA* **86,** 8055–8058.

Rudin C., Lauper U. & Biedermann K. (1991) HIV seroconversion during pregnancy. VII International Conference on AIDS, Florence, June 1991. Astract WC3247.

Tovo P.-A., Palomba E., Gabiano C., Galli L. & Martino M. De (1991) Human immunodeficiency virus type 1 (HIV-1) seroconversion during pregnancy does not increase the risk of perinatal transmission. *Br J Obstet Gynaecol* **98,** 940–942.

Van de Perre P., Simonon A., Msellati P., *et al.* (1991) Postnatal transmission of human immunodeficiency virus type 1 from mother to infant. *N Engl J Med* **325,** 593–598.

British Journal of Obstetrics and Gynaecology
February 1992, Vol. 99, pp. 173–174

BOOK REVIEWS

The Principles of Ultrasonography in Obstetrics and Gynecology Fourth edition edited by A. C. Fleischer, R. Romero, F. Manning, P. Jeanty & A. Everette James. Prentice-Hall International Inc., 1990, London, New Jersey, 668 pages, fully illustrated, £62.00

In Britain, we have been slow to follow the lead of countries such as Australia and to institute a diploma qualification in ultrasound for doctors. Tentative steps have been taken jointly by the Royal College of Obstetricians and Gynaecologists and the Royal College of Radiologists to produce a training programme (without formal qualification) and his has been taken up eagerly by many younger obstetricians and radiologists. These trainees deserve a first class book on ultrasound in obstetrics and gynaecology to match their enthusiasm and commitment and to convey an intelligent, comprehensive and authoritative account of the subject. This is it.

This, the fourth edition of the Principles and Practice of Ultrasonography in Obstetrics and Gynecology, has been extensively revised by an (altered) editorial team of international eminence. There are 44 chapters and 64 authors and, therefore, a considerable potential for repetition. This has been largely avoided by skilful editing.

A particular strength of the book is seen in the chapters on the 'large themes' which are interspersed between those on very specific topics. Thus, the chapters on Normal Fetal Anatomy and Fetal Biometry (both by Philippe Jeanty), on Prenatal Diagnosis of Anatomic Congenital Abnormalities (by Roberto Romero and colleagues) and on the Antenatal Diagnoses of Syndromes (by Beryl Benaceraff) are immensely readable and interesting accounts of topics about which lesser authors could have served up very tedious fare. These large theme chapters provide a background to a specialized account of the ultrasound examination of specific systems or anatomical structures in the fetus (e.g., heart, neck, gastro-intestinal system), specific problems (e.g., the diabetic mother, hydrops fetalis, isoimmunization, intrauterine growth retardation) and various invasive prenatal diagnostic procedures. Newer techniques are discussed in depth, including transvaginal ultrasonography (in both obstetrics and gynaecology) and Doppler ultrasound (a characteristically authoritative by one of the few authors from outwith North America, Brian Trudinger).

If we do develop a British diploma, the trainee will need to have more than a nodding acquaintance with the physics and instrumentation of ultrasound and there are three very clear and comprehensive chapters on these topics. If we also (God forbid) continue to follow the United States down the same path of increasing medico-legal difficulty, we can find no less than three other chapters in the book which address legal issues.

My complaints about the book are very minor compared with its outstanding overall quality and these probably reflect my own biases and interests. I found the chapter on ultrasound of multiple pregnancy to be unusually weak and to contain some antique illustrations. I would like to see more emphasis on the available randomized controlled trials of ultrasound. I could find little about diaphragmatic hernia which seems to have fallen between a number of different stools.

These are minor quibbles about an excellent book. This is, without any doubt the best available text book on ultrasound in obstetrics and gynaecology. It sets the standard for the rest to follow. It is well written and well illustrated and surprisingly inexpensive for its size. It is recommended enthusiastically to all involved in obstetric and gynaecological ultrasound whether they regard themselves as trainees or trainers.

J. Neilson

Nutrition During Lactation, published for the US National Academy of Sciences Institute of Medicine by the National Academy Press, Washington DC, 1991, 309 pages, £30.00. Available from John Wiley & Sons Ltd. 1 Oldham Way, Bognor Regis, West Sussex PO22 9SA

Seldom does the title of a book understate the contents like this. But here is a further compendium of information from subcommittees of the Food and Nutrition Board of the US Institute of Medicine which covers almost every possible aspect of lactation and breast feeding. There are chapters on the epidemiology of breast feeding, nutritional status of lactating women, milk volume and composition, infant outcome related to feeding, and the effect of breast feeding on maternal health.

The treatment of each section is comprehensive and detailed with an up-to-the-minute and critical review of the literature, an admirably clear set of conclusions and sensible recommendations for clinical practice.

For anyone interested in, or working on any aspect of infant feeding, or the care of the lactating woman I can only make one suggestion about this book: get it.

F. E. Hytten

Vaccines for Fertility Regulation (Proceedings of a Symposium on Assessing Safety and Efficacy of Vaccines to Regulate Fertility) convened by WHO Special Programme of Research Development and Research Training in Human Reproduction, Geneva 1989, edited by G. L. Ada & P. D. Griffin. Published on behalf of the World Health Organization by Cambridge University Press, Cambridge 1991, 305 pages, with figures and tables, £65.00

The availability of effective vaccines against infection has been a major factor in reducing the death rate; will vaccines against pregnancy make a significant contribution to reducing birth rates? *Vaccines for Fertility Regulation* is a detailed and well-informed account of the many steps needed to bring a human anti-fertility vaccine to widespread use. Unlike many multi-author books in a specialist area, Ada & Griffin, the editors, have produced a homogeneous work that moves logically through a complex field. It deals with animal models and Loblay and Basten provide an excellent overview of the immune system. The book looks in considerable detail at the possible hazards of human immunization itself, it discusses the requirements for Phase I, II and III trials (down to the level of draft protocols) and Cook & Dickens look at the development of fertility regulating vaccines from the legal and ethical perspective.

The WHO has managed its contraceptive development programme through a series of task forces and *Vaccines for Fertility Regulation* grows out of a expert meeting held in Geneva in June 1989. Vaccine development is one area where the task force approach has a great deal to offer, both because there are a number of places where vaccines could interrupt human reproduction and because the rapidly evolving experience in vaccines against disease can feed into the special problem of fertility regulation. The book ends with the type of detailed consensus statement that WHO does so well from interdisciplinary meetings and it also has an excellent index.

At the time of the meeting Phase I trials of three vaccines against human chorionic gonadotrophin (hCG) were underway. As is well known, if a successful anti-fertility vaccine is to be developed it must be against a molecule that is specific to pregnancy but does not cross-react with any other possible antigen. hCG is an appropriate candidate because placental gonadotrophin differs in its molecular structure from pituitary. Animals studies are also being performed on raising antibodies against sperm and zona pellucida. The latter is a unique and complex structure and the gene for its production has recently been cloned from at least one species. Antibodies to sperm in women are thought to be a cause of infertility that might be replicated artificially. Sperm antibodies of zona pellucida vaccines could be considered genuine contraceptives but hCG vaccines are potential abortifacients and for this reason are explicitly excluded from possible support in the US by the National Institutes of Health (NIH). Cook & Dickens make the valid point that this is one area where the new term *contragestation* describes a valid and useful category of fertility regulation techniques.

The book touches on all candidate antigens, but it is primarily a review of the process of developing a vaccine and to that extent will overlap with the readership of those who, for example, work on anti-HIV vaccines. In order to raise sufficient titre of antibodies a variety of adjuvants are required and progress in other aspects of vaccine development is exceedingly useful and well covered in the book.

The weakness of *Vaccines for Fertility Regulation* is that while it brings together the best scientific advice on all the relevant biological human and ethical problems in vaccines development, it fails to lay out a budget or a timetable for bringing such a product into widespread human use. If this type of meeting had been held by a major multinational pharmaceutical company it would not have been published but it would have led on to management decisions about whether the company was willing to make the investment necessary to carry the work to its conclusions. The very reason that anti-fertility vaccines are not being developed in the private sector is because they are unlikely to be profitable and they would carry a significant medico-legal burden. But if WHO (or other major not-for-profit organisations such as the Population Council or the MRC Unit of Human Reproduction, Edinburgh) are to bring an anti-fertility vaccine into human use then there must be realistic budgets which can be set in front of governments willing to invest in this important area. At a less formal meeting on the same topic in the late 1980s it was estimated it might cost $30m to bring a zona pellucida vaccine to human use.

The amount of money going into contraceptive development is pitifully small (NIH spends 10 cents per capita per annum in the US on contraceptive research and development) and with current levels of investment it is virtually certain that an anti-pregnancy vaccine will not reach human use before the twenty-first century. In a world which increases by one million more births than deaths every 100 hours this is a tragedy. Scientists, however erudite and ingenious, must become more business-like: the cost and schedules of bringing fertility vaccines to a 'go/no-go' state must be analysed and published. Those that are concerned about improving fertility regulation cannot complain of lack of support when they do not even write down what it is they need.

Malcolm Potts

Practical Statistics for Medical Research, D. G. Altman. Chapman and Hall, London, 1990, 611 pages, with figures and tables, £35.00

There is a dearth of well written, moderately priced text books for medical researchers. Douglas Altman's book certainly more than adequately fills this gap.

It is readable and accessible to the non-statistician. I have shown particular chapters to colleagues from a range of backgrounds seeking information about specific topics. Without exception, they have found the way the material is presented helpful in answering their needs, and have come back for more. The numerous examples (many from the field of obstetrics) help to 'ground' the more abstract concepts without loss of general understanding.

The exercises (and even more so, the answers to the questions) were very helpful in testing one's understanding of the contents of the various chapters.

Reading it as a statistician, I did not find the errors that too often bedevil such textbooks, and felt I learned a great deal in some of the areas in which I have not previously specialized. References to further reading were also useful. Inevitably, there are topics which I felt were not addressed in enough depth—for instance, issues of power in clinical trials other than the most common designs. Perhaps some more advanced topics could be dealt with in a sequel?

Diana Elbourne

Books received some of which will be reviewed at a later date

Fetal and Neonatal Physiology edited by Richard A. Polin & William W. Fox. W. B. Saunders Co., Philadelphia, London, Toronto, 1991, Volume I, 1768 pages, fully illustrated. Volume II, 1876 pages, fully illustrated. £200 the set

Fetal and Neonatal Effects of Maternal Disease edited by Avron Y. Sweet & Edwin G. Brown. Mosby Year Book, St Louis, Baltimore, London, 1991, 463 pages with figures and tables, £55.00

The Fetal and Neonatal Brain Stem. Developmental and Clinical Issues edited by M. A. Hanson. Cambridge University Press, Cambridge, New York, Melbourne, 1991, 289 pages with figures and tables, £50.00, US $100

Modern Approaches to Endometriosis edited by Eric J. Thomas & John Rock. Kluwer Academic Publishers, Dordrecht, Boston, London, 1991, 302 pages with figures and tables, £40.00

Molecular Biology for Obstetricians and Gynaecologists by Phillip Bennett & Gudrun Moore. Blackwell Scientific Publications, London, Edinburgh, Boston, 1991, 174 pages fully illustrated with figures and tables, £29.50

Mammography A Guide to Interpretation edited by A. Le Treut & M. H. Dilhuydy. Mosby Year Book, St Louis, 1991, 204 pages fully illustrated, £89.00

A Textbook and Atlas of Integrated Colposcopy by Malcolm Anderson, Joe Jordan, Anne Morse & Frank Sharp. Chapman & Hall, London, New York, 1991, 235 pages, fully illustrated with colour plates, £70.00

Contributions to Obstetrics and Gynaecology Volumes I & II edited by S. S. Ratnam, NG Soon-Chye, D. K. Sen & S. Arulkumaran. Published for the Department of Obstetrics and Gynaecology, National University of Singapore by Longman Singapore Publishers (Pte) Ltd., Volume I 257 pages, volume II 234 pages, with figures and tables. No price given.

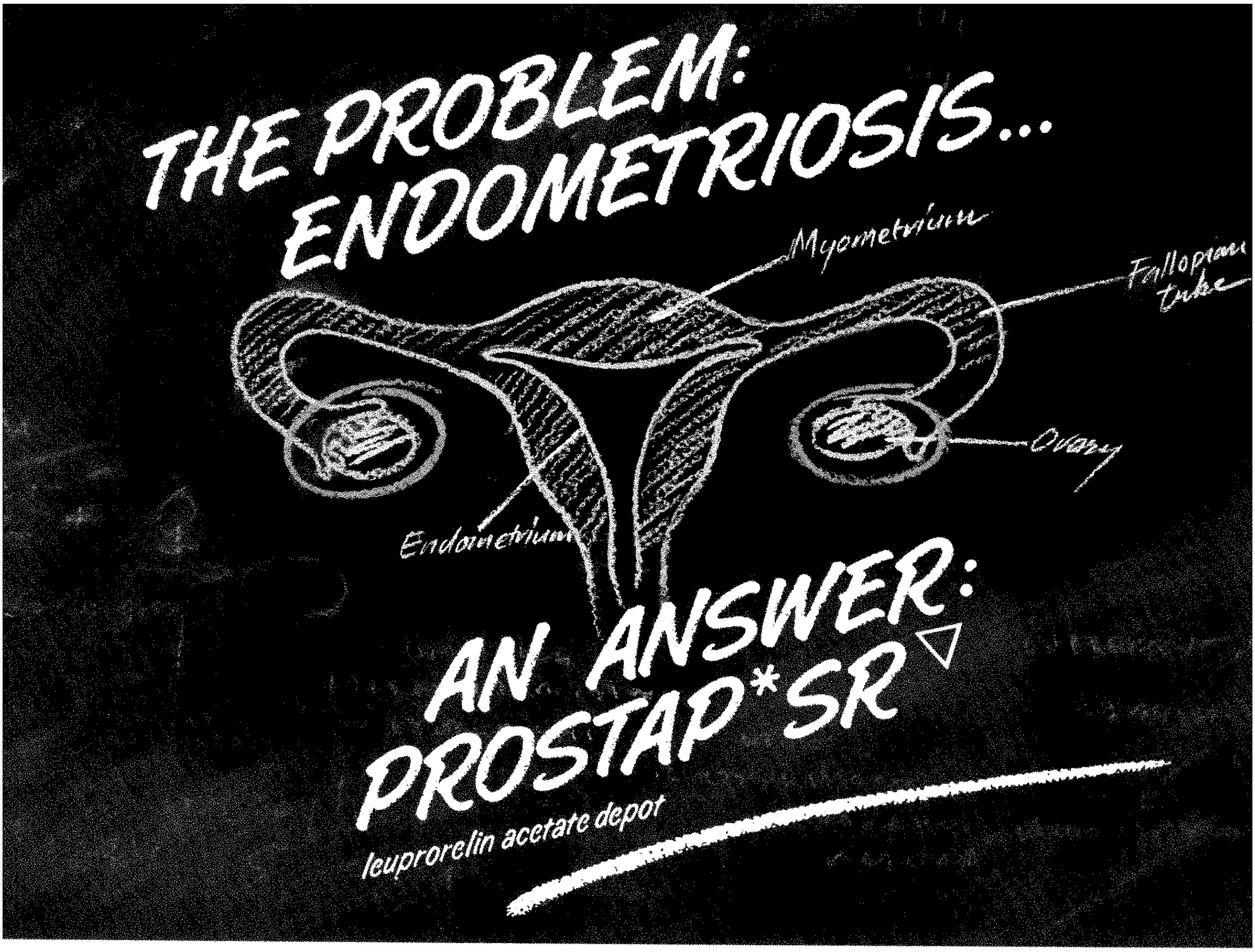
Illustrated Textbook of Obstetrics 2nd edn by Geoffrey Chamberlain, John Dewhurst & David Harvey. Gower Medical Publishing, London, New York, 1991, 263 pages, 300 illustrations, £27.95

Illustrated Textbook of Gynaecology, 2nd edn by V. R. Tindall. Gower Medical Publishing, London, New York, 1991, 192 pages, 300 illustrations, £27.95

Infertility: Your Questions Answered by S. L. Tan & H. S. Jacobs. McGraw Hill Book Co, London, New York, Singapore, 1991, 177 pages, illlustrated, £8.50

The Case for Preconception Care of Men and Women by Margaret Wynn & Arthur Wynn. A. B. Academic Publishers, Bicester, Oxon, 1991, 169 pages, with figures and tables, £29.50

HIV Counselling 2nd edn by Tim Bond. Published by the British Association for Counselling and the Department for Health, in association with Daniels Publishing, Cambridge, 1992, 99 pages, plus a 45-page Index of Agencies, £17.95



Effective GnRH agonist therapy for endometriosis,[1,2] from a simple monthly subcutaneous injection.

A very fine suspension, given through a fine gauge needle, offers patient acceptability and ease of administration in clinic, outpatient or domiciliary use.

PROSTAP* SR ▼

leuprorelin acetate depot

A Logical Approach to Endometriosis

REFERENCES

1. Dlugi AM *et al* Fertility & Sterility 1990; **54** (3) 419-427. (RJG33) **2.** Adashi E *et al*. Data on File, Lederle Laboratories.

ABBREVIATED PRESCRIBING INFORMATION Before prescribing Prostap SR, please refer to full data sheet.

Presentation: Vials containing 3.75mg leuprorelin acetate as microcapsule powder. For reconstitution with Sterile Vehicle, presented in a prefilled syringe. **Indications:** The management of endometriosis, including pain relief and reduction of endometriotic lesions. **Dosage:** 3.75mg administered as a single subcutaneous or intramuscular injection every month for a maximum period of 6 months. Treatment should be initiated during the first 5 days of the menstrual cycle. **Contraindications:** Lactation, pregnancy, undiagnosed abnormal vaginal bleeding. **Warnings:** Whilst ovulation is usually inhibited during therapy, contraception is not ensured, therefore, patients should use non-hormonal methods of contraception. During the early phase of therapy, sex steroids temporarily rise, possibly leading to an increase in symptoms. This, however, dissipates with continued therapy.

Precautions, side-effects: The induced hypo-oestrogenic state results in a small loss in bone density over the course of treatment, some of which may not be reversible. However, during one six-month treatment period, this bone loss should not be important. The generally accepted level of bone loss with LHRH analogues such as Prostap is 5%. For patients with major risk factors for decreased bone mineral content, Prostap therapy may pose an additional risk. Other side effects reported are mainly those related to hypo-oestrogenism; hot flushes, headaches, emotional lability, and vaginal dryness. **Legal category:** POM. **Package Quantities:** Vials containing 3.75mg leuprorelin acetate as microcapsule powder. Prefilled syringes containing 2ml of sterile vehicle. **Basic NHS cost:** £125.40. **Product Licence Numbers:** Prostap SR Powder 3.75mg vials; PL0095/0218. Sterile vehicle prefilled syringes PL0095/0220. Cyanamid of Great Britain.

For further information, see data sheet.

Lederle Laboratories, Fareham Road, Gosport, Hants PO13 0AS.
Tel: (0329) 224000

Lederle Takeda

***Trademark of Takeda**
***Under licence of Takeda Chemical Industries Ltd, Japan.**

British Journal of Obstetrics and Gynaecology

Volume 99 No 2 February 1992

CONTENTS

Commentaries

The dangers of intra-amniotic methylene blue 89
I. McFadyen

Confidence intervals for research findings 90
D. G. Altman & M. J. Gardner

Confined, managed and delivered: the language of obstetrics 92
H. Bastian

Why might maternal serum AFP be high in pregnancies in which the fetus is normally formed? 93
P. A. Boyd

Obstetrics

Breech delivery and epidural analgesia 96
Y. C. Chadha, T. A. Mahmood, M. J. Dick, N. C. Smith, D. M. Campbell & A. Templeton

Pregnancy in sickle cell disease in Bahrain 101
A. M. El-Shafei, J. K. Dhaliwal & A. K. Sandhu

Differences between obstetricians in caesarean section rates and the management of labour 105
J. Guillemette & W. D. Fraser

The treatment of intrahepatic cholestasis of pregnancy by dexamethasone 109
M.-L. Hirvioja & R. Tuimala

Role of prostaglandin in the management of prelabour rupture of the membranes at term 112
T. A. Mahmood, M. J. W. Dick, N. C. Smith & A. A. Templeton

Plasmodium falciparum malaria in pregnancy: a review 118
D. Nathwani, P. F. Currie, J. G. Douglas, S. T. Green & N. C. Smith

Fetal and Neonatal Medicine

Antenatal testing to predict outcome in pregnancies with unexplained antepartum haemorrhage 122
R. A. Ajayi, P. W. Soothill, S. Campbell & K. H. Nicolaides

Second trimester amniocentesis in twin pregnancies: maternal haemoglobin as a dye marker to differentiate diamniotic twins 126
J. R. Beekhuis, H. W. A. De Bruijn, J. M. M. Van Lith & A. Mantingh

Association of moderate obesity with a poor pregnancy outcome in women with polycystic ovary syndrome treated with low dose gonadotrophin 128
D. Hamilton-Fairley, D. Kiddy, H. Watson, C. Paterson & S. Franks

External ocular trauma in instrumental and normal deliveries 132
R. Holden, D. G. Morsman, G. M. B. Davidek & G. M. O'Connor

Doppler umbilical artery flow velocity waveforms in diabetic pregnancy 135
F. D. Johnstone, J. M. Steel, N. G. Haddad, P. R. Hoskins, I. A. Greer & S. Chambers

Jejunal atresia related to the use of methylene blue in genetic amniocentesis in twins 141
J. G. Van Der Pol, H. Wolf, K. Boer, P. E. Treffers, N. J. Leschot, H. A. Hey & A. Vos

Maternal serum screening for Down's syndrome: the effect of routine ultrasound scan determination of gestational age and adjustment for maternal weight 144
N. J. Wald, H. S. Cuckle, J. W. Densem, A. Kennard & D. Smith

Gynaecology

Survey of colposcopy service provided by genito-urinary medicine in England and Wales 150
O. Williams, M. Bodha, D. Hicks & A. B. Alawattegama

Fertility Control

Gynaecologists' abortion practice 153
C. Francome & W. D. Savage

Case Reports

Radical exenterative surgery as the treatment for perineal intraepithelial neoplasia 158
R. A. F. Crawford, J. H. Shepherd, T. Jobling, C. R. Woodhouse & N. Breach

Resolution of pre-eclampsia following intrauterine death of one twin 159
P. Sarhanis & D. H. O. Pugh

Retroperitoneal abscess complicating a normal delivery 160
P. N. Shah, V. A. Rane & A. S. Moolgaoker

Maternal death due to sickle cell chronic lung disease 162
A. Van Enk, G. Visschers, W. Jansen & L. W. Statius Ven Eps

Management of patients with severe hypertriglyceridaemia during pregnancy: report of two cases with familial lipoprotein lipase deficiency 163
G. F. Watts, K. Morton, P. Jackson & B. Lewis

Short Communication

ST-waveform analysis of the fetal electrocardiogram could reduce fetal blood sampling 167
R. B. Johanson, C. Rice, A. Shokr, M. Doyle, R. Chenoy & R. M. S. O'Brien

Correspondence 169

Book Reviews 173

Blackwell Scientific Publications
OXFORD · LONDON · EDINBURGH · BOSTON · MELBOURNE · PARIS · BERLIN · VIENNA
Printed in Great Britain by Headley Brothers Ltd The Invicta Press Ashford Kent and London

Volume 99, Number 3, March 1992

BJOGAS 99(3) 175–274 1992 ISSN 0306-5456

British Journal of Obstetrics and Gynaecology

Edited by David B. Paintin

SUPER ARDUA

Published on behalf of the
Royal College of Obstetricians and Gynaecologists
by Blackwell Scientific Publications

6 reasons why more doctors prescribe Prempak-C and Premarin than any other HRT.

50 YEARS EXPERIENCE

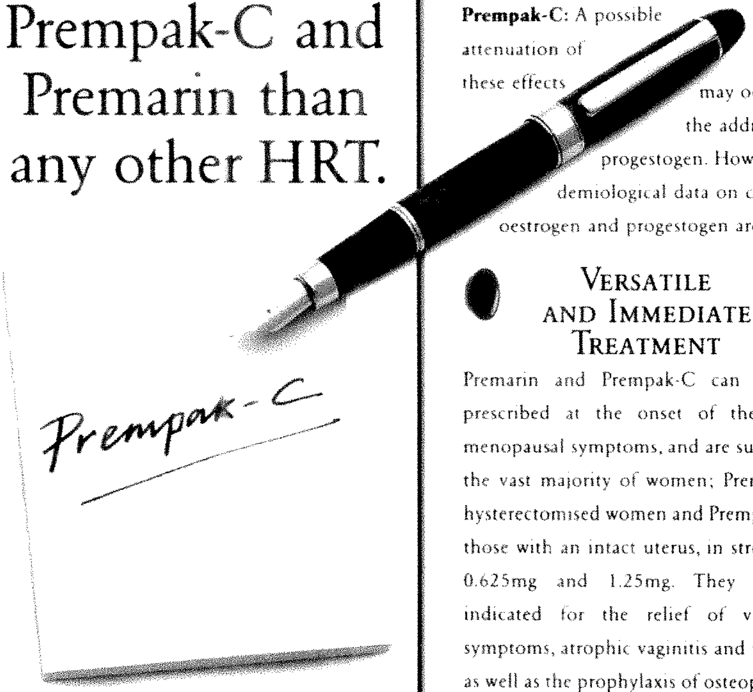
Premarin, a natural conjugated oestrogen, which is also used in the formulation of Prempak-C, is the only oestrogen used in any HRT with 50 years experience. The majority of long term studies, therefore, relate to the conjugated oestrogen found only in these products.

LONG TERM SAFETY - BREAST CANCER?

Both doctors and patients are justifiably concerned about the potential risks of breast cancer for women taking HRT. Whilst there is suggestive evidence of a small increased risk of breast cancer with long-term HRT (greater than 5 years), this varies with the type and dose of the oestrogen used. However, a recent comprehensive review of 31 studies provides evidence that menopausal therapy consisting of 0.625mg/day of conjugated oestrogens does not increase the risk of breast cancer.[1] Most studies, in fact, relate to conjugated oestrogen and so there is insufficient data to arrive at similar conclusions for any other regimen.

PROPHYLAXIS OF OSTEOPOROSIS

Prempak-C and Premarin are both indicated for the prophylaxis of osteoporosis in women at risk of developing fractures. A minimum daily dose of 0.625mg Premarin preserves bone mass, therefore reducing the risk of debilitating injuries such as hip fractures, by up to 66%.[2,3] Further estimates suggest that prescribing Premarin for at least 10 years will reduce the risk of mortality linked to osteoporosis by 60%.[4]



REDUCING CARDIOVASCULAR DISEASE RISKS

Premarin: A recent review of considerable epidemiological evidence has shown, overall, a 50% reduction in risk of coronary disease in oestrogen users. The most common form of oestrogen used in all these studies was conjugated oestrogen, i.e. Premarin.

Prempak-C: A possible attenuation of these effects may occur with the addition of a progestogen. However, epidemiological data on combined oestrogen and progestogen are limited.

VERSATILE AND IMMEDIATE TREATMENT

Premarin and Prempak-C can both be prescribed at the onset of the earliest menopausal symptoms, and are suitable for the vast majority of women; Premarin for hysterectomised women and Prempak-C for those with an intact uterus, in strengths of 0.625mg and 1.25mg. They are also indicated for the relief of vasomotor symptoms, atrophic vaginitis and urethritis, as well as the prophylaxis of osteoporosis in women at risk.

COST EFFECTIVE

Treatment costs are becoming increasingly important, especially as long term therapy can last from 5 to 10 years or longer. Compared to other forms of HRT, Wyeth's products cost remarkably little; Premarin costs just £1.65 and Prempak-C costs £3.98, for 28 days of therapy.[7]

PREMPAK-C
PREMARIN

ABBREVIATED PRESCRIBING INFORMATION

PREMARIN **USES:** Menopausal and post menopausal oestrogen therapy in women without a uterus for vasomotor symptoms, allied disorders such as atrophic vaginitis, kraurosis vulvae, atrophic urethritis, and prophylaxis of osteoporosis in women at risk of developing fractures.
DOSAGE AND ADMINISTRATION: Natural conjugated oestrogens 0.625mg - 1.25mg daily. Continuous administration is recommended. In women with an intact uterus the addition of a progestogen for 10-12 days per cycle is essential.
CONTRA-INDICATIONS: Known or suspected pregnancy and during lactation. History of known or suspected cancer of the breast. Oestrogen dependent neoplasia. Undiagnosed abnormal genital bleeding. Active thrombophlebitis or thromboembolic disorders. Acute or chronic liver disease. Rotor or Dubin-Johnson syndrome. Severe cardiac or renal disease.
WARNINGS AND PRECAUTIONS: Some studies have reported a small increased risk of breast cancer in long term oestrogen replacement therapy users (greater than 5 years), others however have not shown this relationship. It is not known whether concurrent progestogen influences this risk. The risk of endometrial hyperplasia and carcinoma with unopposed oestrogen use is lowered by the addition of a progestogen. Diseases that may deteriorate during therapy include otosclerosis, multiple sclerosis, systemic lupus erythematosis, porphyria, melanoma, epilepsy, migraine and asthma. Use with caution in patients with pre-existing uterine fibroids, endometriosis, breast nodules, fibrocystic disease, and in those with a history of deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction, cardiac or renal dysfunction. Discontinue if jaundice, migraine, visual disturbances, thromboembolic phenomena or significant hypertension develop. Certain endocrine and liver function tests may be affected. Rarely idiosyncratic hypertension may occur. Discontinue treatment prior to surgery or prolonged immobilisation. Gallbladder disease. Insulin requirements may be altered. Premarin is not an oral contraceptive.
SIDE EFFECTS: The following have been reported with oestrogen therapy: premenstrual-like syndrome, increase in size of uterine fibromyomata, vaginal candidiasis, changes in cervical erosion and secretion, cystitis-like syndrome, breast changes, gastrointestinal symptoms, chloasma, melasma, erythema multiforme, erythema nodosum, haemorrhagic eruption, alopecia, hirsutism, steepening of corneal curvature, intolerance to contact lenses, headaches, migraine, dizziness, mental depression, chorea, weight changes, reduced carbohydrate tolerance, aggravation of porphyria, oedema, changes in libido, leg cramps.
PRODUCT LICENCE NUMBERS: Premarin 0.625mg PL0011/0165 Premarin 1.25mg PL0011/0166 Premarin 2.5mg PL0011/0167. **BASIC NHS PRICE:** Premarin 0.625mg £1.65 (28 days). For full prescribing information please refer to data sheet.

PREMPAK-C **USES:** Menopausal and postmenopausal oestrogen therapy for women with an intact uterus for vasomotor symptoms, allied disorders such as atrophic vaginitis, kraurosis vulvae, atrophic urethritis, and prophylaxis of osteoporosis in women at risk of developing fractures.
DOSAGE AND ADMINISTRATION: Natural conjugated oestrogens 0.625mg - 1.25mg daily and one norgestrel 0.15mg tablet should be taken daily from day 17 to day 28 of oestrogen therapy.
CONTRA-INDICATIONS: As for Premarin
WARNINGS AND PRECAUTIONS: As for Premarin. Prempak-C is not an oral contraceptive.
SIDE EFFECTS: As for Premarin. Breakthrough bleeding and spotting. Change in menstrual flow, dysmenorrhoea, amenorrhoea.
PRODUCT LICENCE NUMBERS: Prempak-C 0.625mg PL0011/0161 Prempak-C 1.25mg PL0011/0162.
BASIC NHS PRICE: £3.98 (28 days). For full prescribing information please refer to data sheet.
REFERENCES 1 Dupont W.D and Page D.L. (1991) Arch. Int. Med. 151, 67-72. 2 Lindsay R. et al. (1984) Obstet. Gynecol. 63, 759-763. 3 Kiel D.P. et al. (1987) NEJM, 317, 1169-1174. 4 Ross R.K. et al. (1989) Lancet, I, 505. 5 Stampfer M.J. and Colditz G.A. (1991) Prev. Med, 20, 47-63. 6 Stampfer M.J. et al. (1991) NEJM, 325, 756-762. 7 MIMs February 1992
*Trademark

PREMARIN*
(Conjugated Oestrogens)

Wyeth Laboratories, Huntercombe Lane South,
Taplow, Maidenhead, Berkshire SL6 0PH.

PREMPAK-C*
(Conjugated Oestrogens + Norgestrel)

British Journal of Obstetrics and Gynaecology

Editor: David B. Paintin
Editorial Advisers: F. E. Hytten *London*, I. Chalmers *Oxford*

Assistant editors: Sheila L. B. Duncan *Sheffield*, R. P. Husemeyer *Grantham*

Editorial assistants: Sonja Chayen, Valerie Bolton, Jayne Marchant

Statistical advisers: D. G. Altman *London*, Diana Elbourne *Oxford*, Helen Tate *Saffron Walden*

Editorial board
C.H. Buckley *Manchester*
R.W.I. Cooke *Liverpool*
J.O. Drife *Leeds*
I.D. Duncan *Dundee*
S. Franks *London*
R.B. Fraser *Sheffield*
J.M. Grant *Bellshill*
J.M. McGarry *Barnstaple*
J.P. Neilson *Edinburgh*
R.S. Sawers *Birmingham*
G.E. Smart *Edinburgh*
P.J. Steer *London*
J.W.W. Studd *London*
M. de Swiet *London*
D.W. Warrell *Manchester*

British Journal of Obstetrics and Gynaecology is published on behalf of the Royal College of Obstetricians and Gynaecologists by Blackwell Scientific Publications. The *Journal* publishes reports of original work in obstetrics and gynaecology and related subjects such as human reproductive physiology and contraception; articles reviewing topics in these fields are also acceptable. A section for brief communications, including case reports, allows more rapid publication of papers of not more than 600 words. *British Journal of Obstetrics and Gynaecology* is covered in *Current Contents, ISI/BIOMED, Science Citation Index, Index Medicus, CABS*, and the ADONIS service, whereby copies of individual articles can be printed out from compact disks (CD-ROM) on demand. An explanatory leaflet is available from the publisher.

Books for review
Books for review should be sent to the *British Journal of Obstetrics and Gynaecology*, 27 Sussex Place, Regent's Park, London NW1 4RG.

Correspondence
Letters should be sent to The Editor, *British Journal of Obstetrics and Gynaecology*, 27 Sussex Place, Regent's Park, London NW1 4RG.

As the space available for correspondence is limited, only a selection of letters submitted will be printed. Letters should be brief, factual and related to original work recently published in the *Journal*. The editorial staff reserve the right to shorten letters and make minor corrections. Letters may be published together with a reply from the original author.

Subscription information
The *British Journal of Obstetrics and Gynaecology* is published monthly and annual subscriptions for 1992, accepted on a calendar year basis only, are £90.00 (UK), $165.00 (USA and Canada) and £95.00 (elsewhere), post free. Fellows, Members and successful Part 1 candidates of the Royal College of Obstetricians and Gynaecologists are entitled to subscribe at the special price of £29.00 (UK), £39.00 elsewhere and $68.00, USA and Canada (add $4.76 GST in Canada), also post free. Orders for current subscriptions and back issues should be sent to Blackwell Scientific Publications Ltd, PO Box 88, Oxford OX2 0NE; all other business correspondence, including orders for offprints and advertising space, should be addressed to Blackwell Scientific Publications Ltd, Osney Mead, Oxford OX2 0EL (telephone no. 0865 240201, telex 83355 Medbok G, fax 0865 721205).

Dispatch
The *Journal* is dispatched within Europe by surface mail, to other continents by various forms of air speeded delivery: to the US* by air freight for forwarding by second class post, to India by air freight for guaranteed local delivery, and to all other countries by Accelerated Surface Post.

Copyright and photocopying
Articles published in the *Journal* become its copyright. Reproduction elsewhere, in whole or in part, is not permitted without the previous written consent of the author and editor, and the customary acknowledgments must be made.

© 1992 Blackwell Scientific Publications Ltd. Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by Blackwell Scientific Publications Ltd for libraries and other users registered with the Copyright Clearance Center (CCC) Transactional Reporting Service, provided that the base fee of $06.00 per copy is paid directly to CCC, 27 Congress Street, Salem, MA 01970, USA. 0306-5456/92 $06.00.

This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale. Special requests should be sent to the Editor.

Business correspondence
Orders and remittances relating to subscriptions, back numbers and offprints should be sent to Blackwell Scientific Publications, PO Box 88, Oxford.

Advertisements
Advertisement bookings and enquiries should be sent to the Advertisement Manager, Blackwell Scientific Publications, Osney Mead, Oxford OX2 0EL (Telephone 0865 240201, Fax 0865 721205).

This journal is printed on acid-free paper.

---

* *Postmaster, send address changes to* British Journal of Obstetrics and Gynaecology, *c/o Mercury Airfreight International Ltd, 2323 EF Randolph Avenue, Avenal NJ07001 (US Mailing Agent) Second Class Postage Paid at Rahway NJ.*

Directions to contributors

All papers should be sent to The Editor, *British Journal of Obstetrics and Gynaecology*, 27 Sussex Place, Regent's Park, London NW1 4RG. Papers received and the data they contain are assumed to have been submitted exclusively to the *British Journal of Obstetrics and Gynaecology* and *all* authors must give signed consent to publication in a letter sent with the manuscript The Editor will decide on the time of publication and retains the usual right to modify the style and length of a contribution, major changes will be agreed with the author(s)

Peer review

Manuscripts are subjected to peer review in relation to both the scientific and the statistical content As far as possible the scientific referees are unaware of the authorship and the department of origin of the work. The peer review process takes a minimum of six weeks. Papers that are accepted are published about four to five months later.

Presentation of manuscripts

Three copies of the manuscript and illustrations should be sent. Manuscripts should be typed double spaced on one side of the paper, with wide margins. To facilitate blind refereeing, the names of the author(s), their appointment(s) and their department(s) should be given on a separate front sheet and any acknowledgments on a separate back sheet As far as possible, authors should avoid identifying themselves or their department in the text, but such identification is inevitable in some types of paper. When papers have been accepted for publication, and after any revision has been completed, authors are encouraged to submit the final version on disk This should be IBM compatible An accurate hard copy must accompany each disk, together with details of the type of computer used, the wordprocessing software and the disk operating system The text must not be justified Particular attention should be taken that the final version adheres to the style of the journal in all respects Further details can be obtained from the publishers Authors are advised to keep a copy of all manuscripts, as no responsibility can be accepted for loss.

Reports of original work should usually be arranged in the conventional order of abstract, introduction, methods, results, discussion, acknowledgments and references, with suitable headings for each part. Two further sub-divisions, with appropriately less significant headings, can be used; the third order heading runs on with text at a paragraph opening. Results may be presented in the text, in tables and/or figures, but the text should, in general, comment on rather than repeat information in tables Abstracts are structured and use an appropriate selection of the headings· Objective; Design, Setting, Subjects, Interventions; Main outcome measures, Results, Conclusions Abstracts should not exceed 250 words.

Case reports and short communications do not require a summary or introduction. Short communications should not exceed 600 words and contain no more than one table or figure

Letters to the editor are published only if they comment usefully on material published in previous issues. Letters should not exceed 400 words and must be typed with double line-spacing.

Tables and figures

Tables and figures should be separate from the text, with their positions indicated in the text margin. Both are numbered with arabic numerals Coloured illustrations are used sparingly when these appreciably improve clarity

Figures should be marked on the back (lightly in pencil) only with the name of the paper, the figure number and to indicate the top. Each should have a descriptive legend typed on a sheet separate from the figure. Photographs should be unmounted glossy bromide prints of good contrast.

Figures consist of all material which cannot be set in type, such as photographs, line drawings, etc. Tables are not included in this classification and should not be submitted as photographs Original X-ray films should not be sent—glossy prints must be submitted.

Line drawings should be on white board, arranged to conserve space, and should allow for reduction to 81 mm (single column) or 170 mm (double column). Computer-generated graphics should be printed on good quality plain white paper The layout should be as simple as possible—three-dimensional effects should be used only if this is necessary to express a third variable

Typewritten lettering should not be used on illustrations and explanations should appear in the legend not on the figure itself

Unless written permission for publication from the patient, or the parent or guardian is submitted, the identity of patients in illustrations should be completely concealed by restricting the field to the area of interest or by obscuring the face.

Units and abbreviations

Measurements should be expressed in SI units with the exception of haemoglobin (g/dl) and blood pressure (mmHg). If the original observations were recorded in other units this should be stated, together with the appropriate conversion factors. Standard abbreviations, without punctuation, are used. *Units, Symbols and Abbreviations* (1988) published by the Royal Society of Medicine provides a useful guide. Abbreviations are used sparingly and only if a lengthy name or expression is repeated frequently throughout the manuscript. Words must appear in full on first appearance in both abstract and text, followed by the abbreviation in parenthesis

Drugs are described by their official names but trade names should be indicated in brackets the first time a drug is quoted in the main text.

Statistics

Authors should describe clearly the design of their investigation and the source of the data All statistical methods should be specified so that it is clear which was used where. Papers omitting this information may be returned without review. The basic principle to follow is to supply sufficient information about the design and methods of analysis to allow the research to be repeated by someone else.

The journal has published check lists to guide contributors preparing accounts of certain types of research. These appeared in 1989 (Vol **96**): Bracken M. B , Reporting observational studies, 383–388, Wald N. & Cuckle H., Reporting the assessment of screening and diagnostic tests, 389–396; Grant A., Reporting controlled trials, 397–400

Some points of detail to note are:

(1) It is not acceptable to present the results of a statistical analysis solely by a *P* value—actual results such as means or proportions should always be given, along with the test statistic.

(2) The use of confidence intervals is encouraged.

(3) The symbol ± should not be used when presenting SE or SD. Presentation such as 'the mean . . was 14·2 (SD 3·2) mg' is preferred

(4) When paired comparisons are made it is desirable to indicate the variability of within-pair differences

(5) Unusual methods of analysis should be described and/or referenced

Authors are referred to the general statistical guidelines of Altman *et al.* (1983) for advice about the presentation and interpretation of the statistical aspects of their research.

Altman, D. G., Gore, S. M., Gardner, M. J & Pocock, S. J (1983) Statistical guidelines for contributors to medical journals *Br Med J* **286,** 1489–1493.

Human experiments

Manuscripts should contain a statement that the work was approved by the ethics committee of the institution in which it was done and that subjects gave informed consent to the work. The editors reserve the right to reject papers if they consider the ethical justification to be questionable.

References

In the text, use the name of the author(s) followed by their date of publication; where there are two authors use the form. Smith & Brown 1972; where there are more than two authors use Robinson *et al* 1979.

Arrange the list of authors quoted at the end of the text in alphabetical order set out as follows:

Name(s) and initials of all author(s), year of publication (in brackets), title of the article, name of the journal (abbreviated according to *Index Medicus*), volume number, first and last page numbers In the case of books the order is. Name(s) and initials of author(s), year of publication (in brackets), full title, edition, publisher and place of publisher, page numbers. Where appropriate, the chapter title and the names of the editors should be given.

References to 'personal communications' and 'unpublished work' may be quoted in the text but should not be included in the references Examples of the style to be used are given below

Trudinger B J , Lewis P. J. & Petit B. (1979) Fetal breathing in intrauterine growth retardation. *Br J Obstet Gynaecol* **86,** 432-436.

Hytten F. E. & Leitch I (1971) *The Physiology of Human Pregnancy* 2nd edn, Blackwell Scientific Publications, Oxford, p. 26

Proofs and offprints

Manuscripts should specify the name and address of the author to whom correspondence and page proofs should be sent Only essential corrections can be accepted, more extensive alterations, which may delay publication, will be charged to the author. Fifty offprints of each paper are supplied free, but additional copies may be ordered on the printed sheet sent with the proofs.

British Journal of Obstetrics and Gynaecology
March 1992, Vol 99, pp. 175–181

COMMENTARIES

Audit in gynaecology

The battle hymn of the dis-reorganisers of the new Health Service (nHS) '*Working for Patients*' (Secretaries of State for Health *et al.* 1989a) has been challenged vigorously by most medical professionals and its poorly thought-out ideas exposed. One of the documents that rises above the general level of politically-motivated change is Working paper 6 on *Medical Audit* (Secretaries of State for Health *et al* 1989b). Here professionals in each speciality are invited to make regular assessments of medical performance with the intention of improving the standard of management of patients and the efficiency of the use of resources. Finances will be provided for this development.

In obstetrics we are well versed in this. At a national level, Scotland is an example to us all in data collection, analysis and publication; in the rest of the UK, the Confidential Enquiry into Maternal Deaths (DoH *et al.* 1991) and in the past Perinatal Surveys of the National Birthday Trust (Douglas 1948; Butler & Bonham 1963; Chamberlain *et al.* 1975 and Chamberlain & Gunn 1987) have been useful audits of the maternity services. Locally most hospitals run regular, well attended perinatal and near-miss meetings; between these two levels soon will be slotted the Regional Perinatal Surveys, good examples of which are already found in the North West Thames and in the Northern Regional Health Authorities (Barron 1991).

Gynaecology is a different world. Statutorily-collected data are often inprecise and hard to get while agreed common policies on management are rare even in one hospital. This is in contrast to obstetrics where management protocols are common. In gynaecology individualism reigns; each consultant uses different treatments with multiple variants so a woman admitted to a hospital with three consultants might be cared for under one of four different management plans (the last being what the registrar and SHO really do). To help gynaecological audit, the College has initiated, with funds from the Department of Health, a Medical Audit Unit. This is based in Manchester and directed by Mr Michael Maresh. By offering a data base of already tried audit protocols, they are starting by helping those who want to introduce practical gynaecology audit to minimize the possibility of 300 different units from re-inventing the wheel. Papers on the use of computers and of case notes for gynaecological audit already have been distributed to Fellows and Members for discussion and a meeting was held at the College in the autumn of 1991 The unit is looking at more complex audit subjects and is hoping to develop systems for sub-specialities where there are many diagnostic tests and treatments, and when clinicians have varying views on the most appropriate management, such as infertility.

Audit is concerned not only with optimal care but also with the cost-effective use of limited resources. It is as much about maintaining optimal performance by individual clinicians as about assessing the effectiveness of current management policies. A distinction can be made between audit—ensuring that clinicians carry out existing management protocols efficiently—and clinical research, the development and improvement of management protocols.

A start in gynaecological audit can be made using readily available statistics. As an example, Ferguson *et al.* (1991) showed what can be done with statutorily collected information related to the changes in inpatient episodes in gynaecology over a decade. If their recommendations to district health authorities are adopted, a subsequent examination of the data would show if such changes were effective. This would be good audit procedure for it monitors performance, recommends and implements changes and then remonitors the new system. Other examples that could be applied fairly easily are the extent of use of daycase units in gynaecology or length of stay after standard operations. Observational assessment could be made of the use of the anti-D rhesus prophylaxis after either termination of pregnancy or miscarriage. As an extension of this, with a little extra work, prospective randomization (after informed consent) could be introduced to assess the value of prophylactic procedures such as the usefulness of antibiotics before vaginal surgery or anticoagulants following gynaecological operations.

An area of increasing importance in gynaecology will be the private sector. Although only a small proportion of women use it at present, its influence is likely to increase in the next few years with the contraction in gynaecology in the nHS. At present there is legislation to inspect safety and staffing levels of private hospitals but not to audit the quality of services. It would be wrong to legislate for this, since the doctors who work in both sectors nearly all provide the same standards in public and private care. In consequence it will be by peer-pressure that the private sector will be brought into audit schemes. Already large private hospitals have enrolled voluntarily into the National Confidential Enquiry into Perioperative Deaths and almost certainly they would wish to join in any gynaecological audit that is being done in the nearby nHS hospitals.

Audit is here to stay and whatever we think of the other changes in the nHS, we should support the monitoring of the professional accountability of the care we give individually and collectively. At the lowest level, it may be pandering to consumerism but if services are shown to be inadequate, it could lead to a greater proportion of the budget going to gynaecology At a higher level, peer-controlled audit can tell us what is really going on in this very individualistic branch of medicine; it may improve gynaecological care by showing the value of treatments that may have been put to one side (e.g., medical treatment of dysfunctional uterine haemorrhage) or are new ideas and need rapid, widely applied assessment (e.g., transcervical endometrial resection). Like making love or dinghy sailing, starting is the hardest part. With the help of the regional and district audit committee and the RCOG Audit Unit, gynaecological departments should aim to develop an audit system that matches that used for obstetrics.

Geoffrey Chamberlain *Professor*
St George's Hospital Medical School, London SW19 0RE

References

Barron S. (1991) Audit in Obstetrics. *Br J Obstet Gynaecol* **98**, 1065-1067.

Butler N. & Bonham D. (1963) *Perinatal Mortality. The First Report of the 1958 British Perinatal Mortality Survey*. E. & S. Livingstone, London.

Chamberlain R., Chamberlain G., Howlett B. & Claireaux A. (1975) *British Births 1970 Vol 1 · The First Week of Life*, Heinemann, London.

Chamberlain G. & Gunn P. (1987) *Birthplace*. John Wiley & Son, Chichester

Douglas J. W B. (1948) *Maternity in Britain*. Oxford University Press, Oxford.

Ferguson J. A., Goldacre M. J., Henderson J. & Gillmer M. D. G. (1991) Audit of workload in gynaecology: analysis of time trends from linked statistics. *Br J Obstet Gynaecol* **98**, 772-777.

Secretaries of State for Health, Wales, N. Ireland and Scotland. (1989a) *Working for Patients*. Her Majesty's Stationery Office, London.

Secretary of State for Health, Wales, N Ireland and Scotland. (1989b) *Medical Audit Working Paper 6 in Working for Patients*. Her Majesty's Stationery Office, London, C150 2/89.

Department of Health, Welsh Office, Scottish Home and Health Department, DHSS-Northern Ireland (1991) *Report on Confidential Enquiries into Maternal Deaths in the United Kingdom 1985–87*, HMSO, London.

British Journal of Obstetrics and Gynaecology
March 1992, Vol. 99, pp. 176–178

Aetiology of cerebral palsy

Ideas about the relation between cerebral palsy, intrapartum care and 'birth asphyxia' have become the subject of debate and revision. Problems at or around the time of birth undoubtedly account for some cases of cerebral palsy; what remains unclear is what proportion of all cases of cerebral palsy can be accounted for in this way. The Spastics Society has recently completed a review of much of the current literature around the debate (Lang 1990) and we summarize our findings here.

A number of studies have examined the relation between intrapartum care and cerebral palsy in an indirect way. These time-series studies have investigated trends in rates of cerebral palsy, together with changes in intrapartum care, such as the increase in the number of caesarean sections and the increase in the number of deliveries taking place in hospitals. Despite these developments in obstetric practice aimed at improving care, the prevalence rate of cerebral palsy has not decreased over time. In fact, time-series data for Sweden (Hagberg *et al.* 1989), Ireland (Dowding & Barry 1988), Western Australia (Stanley & Watson 1988), and Britain (Jarvis *et al.* 1985; Pharaoh *et al.* 1987) have shown that rates are either static or increasing.

The putative causal association between intrapartum care, 'birth asphyxia' and cerebral palsy has also been investigated indirectly by examining the relation of indirect markers of asphyxia and long term outcome. These indirect markers include: low Apgar scores, prolonged time before spontaneous breathing, low umbilical vessel pH, abnormal fetal heart rate patterns, and abnormal neonatal neurological signs.

Vitally important to the whole debate is the interpretation of those indicators that have been used to monitor intrapartum fetal distress, and what they actually mean. For example, much store has been placed on the importance of electronic fetal heart tracings. In medical negligence cases, fetal monitoring traces often provide a mainstay to the evidence that expert medical witnesses use in determining whether there was negligence or not. The rationale of fetal heart monitoring is early recognition of fetal complications which, if not treated, could result in cerebral palsy. However, during the years that fetal heart monitoring has been used extensively, there has been a fall in the perinatal death rate, but no fall in the prevalence rate of cerebral palsy. Indeed, as one recent review put it, 'EFM (electronic fetal monitoring) has not been shown to be a reliable predictor of long-term neurologic disorders' (Lumley 1988).

The same uncertainty that surrounds electronic fetal heart monitoring also applies to the Apgar score which is a crude measure of the state of the baby at the time of the birth and, therefore, is a poor predictor of cerebral palsy.

The lack of association between indirect markers of asphyxia and outcome is well summarized in a recent editorial *Lancet* (1989) ' . . . most children with cerebral palsy have not shown these signs neonatally, and most of these indicators are very poor indicators of later neurological abnormality'. Nelson (1988) also concluded that 'Most intrapartum markers, including markers of perinatal asphyxia, are weak predictors of neurologic morbidity, even within the newborn period. Their ability to predict long term status is unknown for most, and poor for those for which data are available.'

Another approach has been to estimate the likelihood that neurologic injury has happened at the time of birth, using some of the above mentioned indicators. The National Collaborative Perinatal Project (NCPP), administered by the National Institute of Neurological and Communicative Disorders and Stroke, examined approximately 41 000 children born in 12 urban teaching hospitals in the United States. This cohort study examined prenatal, perinatal and postnatal data for each pregnancy, as well as considering socio-economic factors and maternal history. At 7 years of age 189 of these children were known to have cerebral palsy, and only 21% of them had at least one indication that there had been intrapartum asphyxia. However, one third of these children also had a major malformation not connected to the CNS (Nelson & Ellenberg 1986). In total, over half the children with cerebral palsy who had some indication of 'asphyxia' also had evidence of problems in the period before labour. This study estimated that the proportion of cerebral palsy that can be accounted for by intrapartum asphyxia ranged between 3 and 13%.

The results of the NCPP study are supported by research reported by Stanley & Watson (1988) in Western Australia. Their data were collected from a register of people with cerebral palsy, which has been regularly updated since 1956. A case-control study was conducted comparing 183 children with cerebral palsy and matched controls born between 1975 and 1980. Only 4·9% of the children with cerebral palsy were thought to have experienced intrapartum injury, and in a further 3·3%, intrapartum injury was considered possible.

On the basis of these estimates it seems reasonable to conclude that intrapartum asphyxia may account for not more than 10% of cerebral palsy.

Freeman & Nelson (1988) conclude that 'Most cerebral palsy is of unknown cause, and when a presumed cause can be identified, it more often occurs prior to the onset of labour'. Only when there has been severe, prolonged hypoxia, which has not killed the baby, do an important minority of survivors go on to manifest cerebral palsy.

In order to affirm that the 'brain damage' is the result of asphyxia, Freeman & Nelson (1988) maintain that the following questions should be answered positively:

(i) Is there evidence of marked and prolonged intrapartum asphyxia?
(ii) Did the infant, as a newborn, exhibit signs of moderate or severe hypoxic-ischaemic encephalopathy during the newborn period, with evidence also of asphyxial injury to other organ systems?
(iii) Is the child's neurologic condition one that intrapartum asphyxia could explain?
(iv) Has the work-up been sufficient to rule out other conditions?

A clearer association than that between birth asphyxia and cerebral palsy is the association between preterm birth and cerebral palsy. Approximately 20% of children with cerebral palsy were very immature at birth (less than 32 weeks gestation) (Johnson & King 1989). Immature newborn infants are particularly susceptible to haemorrhage into and ischaemia of brain tissue. This can lead either to death, or to permanent damage which will later be manifested as cerebral palsy. With developments in life support systems in neonatal intensive care, more of these tiny babies are surviving, and the frequency of cerebral palsy among them is increasing (Pharaoh 1990).

The view that cerebral palsy is not the result of birth asphyxia, but is in all probability caused sometime during pregnancy or after delivery in immature infants, is beginning to be accepted more widely. If this new orthodoxy becomes accepted then there are clearly repercussions for parents suing through the Courts for damages, health authorities and the legal profession.

These implications are, however, more complex than many commentators have so far grasped.

We cannot assume that all claims for negligence can now be simply thrown aside. In any particular case before the courts there is no way of knowing if it involves one of the 5–15% of births that may have been damaged at or around the time of birth. The balance of probabilities would still have to be considered for each case in question, even if the general assumptions about causation have changed.

Faced with the fundamental flaws in the present legal system many commentators have advocated a system of no-fault compensation to support cases of damage at birth. Yet this assumes that 'no fault' is the same as 'no cause'. All the schemes so far proposed decide on eligibility for compensation by showing that medical intervention was the cause of the disability. 'No fault' compensation is not 'no cause' compensation, and therefore, the schemes proposed thus far run into the same problems as the current legal system. The identification of cause is still the key issue.

The latest report from the Royal College of Physicians (1990) recognizes this crucial point in its report on compensation for adverse consequences of medical intervention and follows the logic of the argument by recommending a comprehensive disability income.

A variant of these schemes that seems to have found particular favour with the Chief Medical Officer is the State of Virginia's scheme, which set up a fund to provide immunity to negligent obstetricians for compensating neurologically impaired babies. Forty infants a year were supposed to be compensated. After 3 years of operation none had been compensated as all claims had foundered on the tight definitions of causation incorporated into the scheme. It is reasonable to believe that should such a scheme be introduced in this country the main attraction would be for the Treasury, not for people with cerebral palsy.

One conclusion recommended by all commentators who have looked at the problem is to move quickly towards a comprehensive disability income scheme that would properly support parents and disabled children. This still seems to us the best hope for disabled people.

One element that should not be forgotten is that for many parents the overriding need is to know exactly what happened. This should not be forgotten in any future legal or profession arrangements that review the performance of the medical profession.

The Spastics Society will shortly be issuing a discussion paper 'Paying for Disability' dealing with these issues in more detail. For a copy please contact the authors at the Campaigns Department, The Spastics Society, 12 Park Crescent, London W1N 4EQ.

Brian Lamb
Head of Campaigns and Parliamentary Affairs
Raymond Lang
Fast Track Project
The Spastics Society
12 Park Crescent
London W1N 4EQ

References

Dowding V. M & Barry C. (1988) Cerebral palsy: changing patterns of birthweight and gestational age (1976–81). *Ir Med J* **81**, 25-29.

Freeman J. & Nelson K. (1988) Intrapartum asphyxia and cerebral palsy. *Pediatrics* **82**, 240-249.

Hagberg B., Hagberg I., Onlow I. & Von Wendt L. (1989) The changing panorama of cerebral palsy in Sweden V: The birth year period 1979–82. *Acta Pediat Scand* **78**, 283-290.

Jarvis S. N., Holloway J. S. & Hey E. N. (1985) Increase in cerebral palsy in normal birthweight babies. *Arch Dis Child* **60**, 1113-1121.

Johnson A. & King R. (1989) A regional register of early childhood impairments: a discussion paper *Community Medicine* **11**, 352-383.

Lancet (1989) Cerebral palsy, intrapartum care, and a shot in the foot. *Lancet* **ii**, 1251-1252.

Lang R. (1990) *Medical Negligence and Cerebral Palsy* The Spastics Society, London.

Lumley J. (1988) Does continuous intrapartum fetal monitoring predict long-term neurological disorders? *Paediatr Perinat Epidem* **2**, 299-307

Nelson K. (1988) What proportion of cerebral palsy is related to birth asphyxia? *J Pediatr* **112**, 572-574.

Nelson K. & Ellenberg J. (1986) Antecedents of cerebral palsy; multivariate analysis of risk. *New Engl J Med* **315**, 81-86.

Pharaoh P. O. D., Cooke T, Rosenbloom L. & Cooke R. (1987) Trends in birth prevalence of cerebral palsy. *Archives of Disease in Childhood* **62**, 379-82.

Pharaoh P. O. D., Cooke T., Rosenbloom L. & Cooke R. (1990) Birthweight specific trends in cerebral palsy. *Arch Dis in Child* **65**, 602-606.

Royal College of Physicians (1990) *Compensation for Adverse Consequences of Medical Intervention*. Royal College of Physicians, London.

Stanley F. J. & Watson L. (1988) The cerebral palsies in Western Australia; trends 1968 to 1981. *Am J Obstet Gynecol* **158**, 89-93.

British Journal of Obstetrics and Gynaecology
March 1992, Vol. 99, pp. 178–180

Therapeutic uses of transcervical catheterization of the fallopian tubes

With the trend towards minimally invasive operative procedures in gynaecology it is not unnatural that investigators should look towards non surgical techniques to gain access to the female reproductive tract. Transcervical catheterization of the fallopian tube is currently being assessed in three areas of gynaecological practice: proximal tubal occlusion, ectopic pregnancy and assisted conception.

Transcervical tubal catheterization is usually performed as an outpatient procedure. An introducer is passed through the cervix and advanced to the uterine fundus. Usually the introducer has a terminal curve so that it can be orientated towards the cornua. A coaxial catheter of smaller diameter can then be passed through the introducer directly into the fallopian tube. Sometimes a soft metal guidewire is threaded through the inner catheter. The correct placement of the catheter in the tube can be verified by radiological or ultrasound screening.

Transcervical tubal catheterization was first performed a quarter of a century ago (Corfmann & Taylor 1966) but only became a practical therapeutic technique for recanalizing proximally occluded tubes in the middle of the last decade (Platia & Krudy 1985). Confino *et al.* (1986) first described balloon tuboplasty using a modification of the technique of balloon angioplasty. In a recent muticentre study of transcervical balloon tuboplasty in 77 women (Confino *et al.* 1990) at least one tube was recanalized in 92%, and 34% of the women who did not have coexisting distal tubal occlusion achieved a clinical pregnancy with a median follow up of 1 year. Only one woman had an ectopic pregnancy. Complications were recorded in two women (3%) both involving pin point perforations of the tube by the metal guidewire with no clinical sequelae. An alternative technique pioneered by Rösch *et al.* (1988) involves dilating the proximal tube using a series of coaxial catheters of increasing diameters. A similar high success rate of tubal recanalization was recorded (96%). This study also illustrated that this procedure is unsuitable for treatment of midisthmic obstruction as a perforation rate of 50% was reported. Subsequent series have confirmed the reproducibility of these results (Capitanio *et al.* 1991; Segars *et al.* 1990). The ease with which tubal recanalization is achieved gives some insight into the nature of the tubal pathology. In a histological study of fallopian tubes in 18 patients undergoing resection for proximal tubal obstruction, Sulak *et al.* (1987) confirmed occlusion only in seven women. The remainder had patent tubes although in six women an amorphous cast including inflammatory cells was present within the lumen. If proximal tubal obstruction is diagnosed at laparoscopic hydrotubation and the diagnosis is confirmed at hysterosalpingography, it would be prudent in the future to consider transcervical tubal catheterization before opting for the alternatives of tubo-cornual reanastomosis or in vitro fertilization.

The procedure is also being explored as a method of facilitating tubal transfer of gametes, zygotes and embryos in assisted conception (Jansen & Anderson 1987). The tubal environment is known to be favourable for fertilization and early embryonic cleavage. Gamete intrafallopian transfer (GIFT) and zygote intrafollicular transfer (ZIFT) are now recognised as realistic alternatives to in vitro fertilization and embryo transfer (IVF-ET) in patients with patent fallopian tubes. Whereas intrauterine embryo transfer is a simple and relatively non-invasive procedure with few untoward effects, the tubal transfer of gametes or zygotes requires laparoscopy under general anaesthesia. Technically it is not difficult to cannulate the tubal ostium transvaginally but before transcervical tubal catheterization can be considered as an acceptable clinical alternative to laparoscopic GIFT or ZIFT, it must be demonstrated convincingly that the procedure is not associated with a reduction in the pregnancy rate. Most of the work in this area has assessed the pregnancy rate after the transcervical tubal transfer of 2-day embryos (Diedrich *et al.* 1991; Risquez 1990a). In the largest series Diedrich *et al.* (1991) attempted transvaginal tubal embryo transfer in 118 women with successful cannulation in 84%. Twenty-nine pregnancies were reported in 95 transfers (31%). As comparable results can be achieved by conventional intrauterine embryo transfer the attraction of tubal embryo transfer is not immediately apparent (Forman *et al.* 1991). More interestingly Ferraiolo *et al.* (1991) performed outpatient GIFT by combining transvaginal oocyte retrieval and transvaginal tubal transfer of gametes. Seven pregnancies were achieved in 26 women undergoing oocyte retrieval (27%). Pregnancy was also reported in 8 of 25 patients (32%) undergoing transvaginal tubal transfer of zygotes (Scholtes *et al.* 1990). More information is required, notably on the diameter of catheter to be used, the volume of fluid to be injected with the gametes, the frequency of tubal pregnancy as well as immediate side effects such as tubal infection. Nevertheless, these studies are significant as they demonstrate that outpatient GIFT is a practical proposition for the future. By obviating the need for operating theatre resources GIFT treatment could become more widely available.

The most recent application of transcervical tubal catheterization is in the diagnosis and treatment of tubal ectopic pregnancy. Gynaecologists in the UK are generally more aggressive in their management of tubal pregnancy than their colleagues in Europe and the United States, probably because operative laparoscopy is less widespread in this country. There are now several studies showing that even conservative surgery may be superseded by non surgical management in selected cases. This has been the subject of several recent reviews (Saunders 1990; Cannon & Jesionowska 1991; Pansky *et al.* 1991; Drife 1990). The most common technique involves injecting methotrexate into the tubal gestational sac at laparoscopy (Pansky *et al.* 1989) or through the vaginal vault under ultrasound control (Feichtinger & Kemeter 1987). This latter method depends on the ability to identify a gestation sac. Furthermore there is a small risk of damaging vascular structures. Risquez *et al.* (1990b) have recently described a method of diagnosing tubal ectopic pregnancy by transcervical tubal catheterization and then administering methotrexate through the catheter around the implantation site. This has the advantage of being atraumatic and is practicable even in the absence of a distinct tubal gestation sac. We are currently participating in a multicentre study to assess the efficacy of this technique and the occurrence of subsequent tubal patency. Transcervical tubal catheterization is contraindicated in the presence of significant haemoperitoneum or haemodynamic disturbance and is unlikely to be effective if a fetal heart is demonstrated or the serum β-hCG level is over 5000 m-IU/ml at the time of treatment.

Other potential applications for transcervical tubal catheterization are in the field of contraception. In China considerable experience has been gained using this method for non operative, reversible female sterilization (Sheng-cai 1990). This has not yet been investigated in the West. The recent development of falloposcopy, enabling the whole length of the fallopian tube to be observed under direct vision is another variation of tubal catheterization which is already yielding new information about tubal structure and function (Kerin *et al.* 1990). Transcervical tubal catheterization is an easily acquired technique which provides access to the lumen of the fallopian tube, one of the most hidden sites in the female reproductive tract. As so much gynaecological pathology arises within the tube, this is a technical development which deserves more thorough investigation.

R. G. Forman
Senior Lecturer
Reproductive Medicine
M. G. Chapman
Professor Obstetrics and Gynaecology
Department of Obstetrics and Gynaecology
Guy's Hospital, London SE1 7EH

References

Cannon L. & Jesionowska H. (1991) Methotrexate treatment of tubal pregnancy. *Fertil Steril* **55,** 1033-1038.

Capitanio G. L. Ferraiolo A. F., Croce S., Gazzo R., Anserini P. & Ceco L. (1991) Transcervical selective salpingography: a diagnostic and therapeutic approach to cases of proximal tubal injection failure. *Fertil Steril* **55,** 1045-1050.

Confino E, Friberg J. & Gleicher N. (1986) Transcervical balloon tuboplasty. *Fertil Steril* **46,** 963-966.

Confino E., Tur-Kaspa I, DeCherney A. *et al.* (1990) Transcervical balloon tuboplasty: a multicentre study *JAMA* **264,** 2079-2082.

Corfmann P. A. & Taylor H. C. (1966) An instrument for transcervical treatment of the oviduct and uterine cornua *Obstet Gynecol* **27,** 880-884.

Diedrich K., Bauer O., Werner A., van der Ven H., Al-Hasani S. & Krebs D (1991) Transvaginal intratubal embryo transfer a new treatment of male infertility. *Human Reprod* **6,** 672-675.

Drife J. O. (1990) Tubal pregnancy. *Br Med J* **301,** 1057-1058.

Feichtinger W & Kemeter P. (1987) Conservative treatment of ectopic pregnancy by transvaginal aspiration under sonographic control and methotrexate injection. *Lancet* **i,** 381-382.

Ferraiolo A., Croce S., Anserini P, Reorgida V., Lanera P., Capitanio G. L. & de Cecco L. (1991) 'Blind' transcervical transfer of gametes in the Fallopian tube: a preliminary study. *Human Reprod* **6,** 537-540.

Forman R G., Robinson J, Egan D., Ross C., Gosden B. & Barlow D. H. (1991) Follicular monitoring and outcome of in vitro fertilization in gonadotropin-releasing hormone-agonist treated cycles *Fertil Steril* **55,** 567-573.

Jansen R P. S. & Anderson J. C. (1987) Catheterization of the fallopian tubes from the vagina *Lancet* **ii,** 309.

Kerin J, Daykhovsky L., Segalowitz J. *et al.* (1990) Falloposcopy: a microendoscopic technique for visual exploration of the human fallopian tube from the uterotubal ostium to the fimbria using a transvaginal approach. *Fertil Steril* **54,** 390-400.

Pansky M., Bukovsky I., Golan S. A, Langer R., Schneider D., Arieli S. & Caspi E. (1989) Local methotrexate injection: a nonsurgical treatment of ectopic pregnancy. *Am J Obstet Gynecol* **161,** 393-396.

Pansky M, Golan A., Bukovsky I. & Caspi E. (1991) Non surgical management of tubal pregnancy. *Am J Obstet Gynecol* **164,** 888-895.

Platia M. P. & Krudy A G. (1985) Transvaginal fluoroscopic recanalization of a proximally occluded oviduct. *Fertil Steril* **44,** 704-706.

Risquez F., Boyer P., Rolet F., Magnani M., Guichard A., Cedard L. & Zorn J. R. (1990a) Retrograde tubal transfer of human embryos. *Human Reprod* **5**, 185-188.

Risquez F., Mathieson J., Pariente D. *et al.* (1990b) Diagnosis and treatment of ectopic pregnancy by retrograde selective salpingography and intraluminal methotrexate injection: work in progress. *Human Reprod* **5**, 759-762.

Rosch J., Thurmond A. S., Uchida B. T. & Sovak M. (1988) Selective transcervical fallopian tube catheterization: technique update. *Radiology* **168**, 1-5.

Saunders N. J. StG. (1990) Non-surgical treatment of ectopic pregnancy. *Br J Obstet Gynaecol* **97**, 972-973.

Scholtes M. C. W., Roozenburg B. J., Alberda A. T. & Zeilmaker G. H. (1990) Transcervical intrafallopian transfer of zygotes. *Fertil Steril* **54**, 283-286.

Segars J. H., Herbert C. M., Moore D. E., Hill G. A., Wentz A. C. & Winfeld A. C. (1990) Selective fallopian tube cannulation: initial experience in an infertile population. *Fertil Steril* **53**, 357-359.

Sheng-cai Z. (1990) Non-operative and reversible fallopian tube occlusion: clinical experience in China. VII World Congress on Human Reproduction. Helsinki, June 26-July 1. Abstr 639.

Sulak P. J., Letterie G. S., Coddington C. G., Haysip C. C., Woodward J. E. & Klein T. A. (1987) Histology of proximal tubal occlusion. *Fertil Steril* **48**, 437-440.

British Journal of Obstetrics and Gynaecology
March 1992, Vol. 99, pp. 180–181

Role of the senior house officer in the labour ward

The role of the senior house officer (SHO) in the labour ward has evolved without formal planning so that the SHO acts as an intermediary between the midwife, the registrar and the consultant. They are the staff who are immediately available, working long hours, clerking in every woman who arrives in labour, putting up drips, rupturing membranes, topping-up epidurals, suturing perineums and doing anything else that more senior doctors or midwives consider to be outside their personal view of their own job description.

There may be no formal protocol agreed between the consultants, and learning can be only by osmosis from midwives and registrars. Previous SHOs may have left instructions on how the department runs and these may have been debased by passage of time. The hours of work are often in excess of 90 hours per week. We can all remember this stage of our own careers and it is necessary that it is now being questioned. There is no doubt that this form of working is totally inappropriate to modern day obstetric management, particularly in relation to normal pregnancy and delivery.

A modern SHO has completed at least two house officer posts, each of six months, since qualification, and maybe more. The majority are planning to become general practitioners, either through vocational training schemes or through a succession of appointments they will organize for themselves. Their view of their need for knowledge of intrapartum care depends on whether they propose to look after their patients completely during pregnancy and labour, if they are normal, or whether they plan only to provide antenatal and postnatal care.

Doctors who provide care for pregnant women need a comprehensive postgraduate experience of obstetrics, whether they are to be general practitioners or hospital specialists. The appearance of a general practitioner's name on the obstetrics list should imply formal postgraduate training, confirmed by examination. SHOs who are planning a career in obstetrics and gynaecology need similar basic training and experience but must also be encouraged to deepen their interest in the speciality during this foundation phase of their training. This group needs nurturing if they are to retain their vocational drive and career intention.

Midwives are practitioners in their own right and are liable under the law for their professional actions. They now undergo a longer training and are skilled in looking after healthy women in normal pregnancy and labour. SHOs can learn a great deal from the midwives and this should be encouraged, but there can be a midwife/doctor barrier. Each unit must encourage the break-down of this barrier to the mutual benefit of doctors, midwives and pregnant women. Senior obstetricians have been slow to realize that midwives are competent professional colleagues in their own right and that midwifery care is now totally different from when they were SHOs.

The labour ward is a stressful and frightening place to a new SHO just beginning obstetrics (RCOG 1991). They will have heard frightening stories from their colleagues and may have witnessed scenes of emergency during their medical student days. No consideration is taken of the feelings of SHOs when they first step into a labour ward and it is important that they have a proper induction period in their first week during which they gain familiarity with labour ward procedures without feeling they are expected to assume responsibility. SHOs should be encouraged to consider midwives as equals but with a different role in obstetric care. Midwives should be encouraged to involve the SHOs in the management of women in labour and not to bypass them. In fact, a midwife has skills the SHO needs to acquire and the SHO should accept the combined role of trainee and colleague. Protocols for the management of clinical problems in the labour ward should be agreed between consultants and midwives and it is important that consultants come to the labour ward regularly and utilize clinical events to teach the fledgling SHO, and to reinforce the application of the protocol.

Practices are changing. Midwives are taking more responsibility and may have a broader range of practical skills, such as perineal suturing. the siting of intravenous drips, giving intravenous drugs and topping up of epidurals. They are able to decide what is normal and what is abnormal and make decisions with regard to the need for obstetric intervention. This may make SHOs feel threatened if they have been conditioned to consider themselves as being in charge of the labour ward, with resulting resentment and loss of interest in obstetrics.

It is therefore important that every department defines the clinical roles of their medical and midwifery staff and how the need for training and for clinical care can be combined within reasonable working hours for each grade. It is better for a skilled, experienced midwife to suture a perineum rather than for this to be done by a new SHO who may have had little or no experience as a medical student. The SHO should acquire practical skills both from midwives and from assisting the registrar or consultant; they should not learn by their mistakes.

Consultants and senior registrars need to assess the training requirements of each SHO, and to fit the theoretical training and practical experience to the trainee's future, rather than just using the SHO as a pair of hands. Midwives should be encouraged to teach SHOs normal obstetric practice. The role of the SHO should be to provide liaison between the midwife and the registrar and consultant, as well as the assessment and management of obstetric abnormalities. Clear guidelines that specify the roles of staff should be laid down for all in each department so that there is co-operation rather than confrontation. The Heads of Agreement paper (Department of Health, Welsh Office, DHSS-Northern Ireland, Scottish Home and Health Department 1990) contains suggestions as to how this may be approached.

A joint RCOG/RCPG Working Party (1992) recommends sufficient opportunities during training for the learning of normal labour and that midwives should contribute to this training programme. This could be done quite easily during daylight hours. Training should be constructed to build up confidence and overcome disincentives to involvement in intrapartum care. This requires a different attitude towards training. If a vocational trainee wishes to contribute to intrapartum care, he should be specially trained to do this. This could mean an extra six months in obstetrics and gynaecology, a total of one year of combined training. Six months of combined training will be sufficient for those who, as general practitioners, plan to provide only antepartum and postpartum care but such SHOs would need sufficient experience of performing normal deliveries and of observing instrumental deliveries. They would need to keep log books of their experience and these would need to be inspected specifically every 2 months to ensure that appropriate training had occurred. Attendance at antenatal and, particularly, post-natal clinics would be essential and experience of contraceptive provision should be obtained under the supervision of a family planning training doctor.

Obstetrics and gynaecology is one of the most stressful specialities in medicine and this must be recognized when staffing levels are determined. There is a paper by McKee *et al.* in this issue of the Journal (p. 197) which addresses the amount of work an SHO really needs to do between 1700 and 0900 hours in relation to normal pregnancy and normal labour. The authors do not propose a reduction in the number of hours on call but do suggest ways in which the number of calls during the night may be reduced, so reducing the stress levels to which these young doctors are subjected. The Government has suggested that each unit looks at ways in which it can reduce hours on duty (Department of Health *et al.* 1990). One, of course, is to increase the number of staff, but this is not always possible. A way of improving the situation is to reduce the number of calls. Units that provide organized training and who strive to ease the burden borne by SHOs will encourage able young trainees to remain in the speciality.

J. R. Pogmore
Consultant Obstetrician & Gynaecologist
Chairman: Hospital Recognition Committee
Royal College of Obstetricians & Gynaecologists
27 Sussex Place, Regent's Park
London NW1 4RG

References

Department of Health, Welsh Office, DHSS-Northern Ireland, Scottish Home and Health Department (1990) *Heads of Agreement Ministerial Group on Junior Doctors' Hours*, DoH, London.

Joint RCOG/RCGP Working Party (1992) *Recommendations for General Practitioner Vocational Training in Obstetrics and Gynaecology*, RCOG (in press).

McKee M., Priest P., Ginzler M. & Black N (1992) Can out-of-hours work by junior doctors in obstetrics be reduced? *Br J Obstet Gynaecol* **99**, 197-202.

RCOG (1991) *Guidance on Labour Ward Practice*, RCOG, London.

British Journal of Obstetrics and Gynaecology
March 1992, Vol. 99, pp. 182–185

OBSTETRICS

Objective measurement of anxiety in hypertensive pregnant women managed in hospital and in the community

W. CARTWRIGHT
Research Associate
K. J. DALTON
University Lecturer and Consultant
H. SWINDELLS
*Midwifery Research Sister**
S. RUSHANT
Midwifery Research Sister
P. MOONEY
Research Registrar†

Perinatal Research Group, Department of Obstetrics and Gynaecology
University of Cambridge
Rosie Maternity Hospital
Cambridge CB2 2SW

ABSTRACT

Objectives To determine whether pregnant hypertensives women are more anxious when monitored in hospital or at homes.

Design Prospective randomized controlled trial.

Setting Rosie Maternity Hospital and women's homes.

Subjects Ninety-nine pregnant hypertensive women: 50 had their blood pressure measured telemetrically from home, and 49 had it measured in hospital.

Main outcome measures Number of episodes of monitoring, duration of monitoring, mean blood pressure during monitoring, gestational age at delivery, trait and state anxiety levels.

Results There were no significant differences in anxiety levels, or in any other outcome measure, between the home and hospital groups.

Conclusion When blood pressure is being monitored serially in pregnant hypertensive women, there is no measurable difference in their anxiety levels, whether they are in hospital or at home.

Initially, when a pregnant women is found to be hypertensive, it may be difficult to tell whether this is transient and stress-related, or if it heralds more serious disease. An immediate problem arises: should she be admitted to hospital for observation, or should her blood pressure be managed in the community?

It is widely believed that hospital admission causes stress, and several workers have demonstrated associated changes, both of a physiological and psychological nature (Volicer & Volicer 1978; Volicer 1978; Mason *et al.* 1965; Wilson-Barnett 1978; Hugh-Jones *et al.* 1964). Admission for hypertension is likely to be particularly stressful in late pregnancy, as most women feel perfectly well, and view hospitalization as a frustrating and negative experience (Merkatz 1978). Indeed, such antenatal admission could be viewed as a 'crisis within a crisis', which interferes with the emotional and practical preparations that are necessary for delivery (Rubin 1975; Budd 1977; White & Ritchie 1984). Thus, on these grounds alone, it could be argued that admission is best avoided whenever possible.

Hypertension has come to be the commonest reason for antenatal admission, and is a major cause of maternal mortality. (Department of Health 1989). By extrapolating from admissions in Cambridge, we estimate that about 70 000 such women are admitted to hospital in Britain each year. Although some women need to be admitted, most could probably remain at home if they could test their own urine for protein, and if their blood pressures could be monitored telemetrically.

Such a blood pressure telemetry system has been developed in Cambridge, and it has enabled many pregnant hypertensive women to stay at home (Dalton *et al.* 1987).

In normotensive pregnancies, Swindells *et al.* (1990) have already shown that women can easily use such a system, and that it does not cause them any undue anxiety, regardless of their socio-demographic background, or their previous experience with electronic equipment.

We have been conducting research on various clinical and psychological issues relating to the use of blood pressure telemetry in pregnancy (Mooney *et al.* 1991). Here we report on how hypertensive pregnant women reacted on their use of the Cambridge blood pressure telemetry system, particularly in terms of their level of anxiety, which we measured objectively.

Subjects and methods

The Cambridge blood pressure system

This consists of a standard Dinamap 1846SX blood pressure

Correspondence: W. Cartwright.
*Now Research Nurse, Dunn Nutrition Unit, Milton Road, Cambridge.
†Now Senior Registrar in Obstetrics & Gynaecology, South Cleveland General Hospital, Middlesbrough.

monitor, linked to a controlling microprocessor fitted with a small screen and three patient-response buttons. The system is fully automated and takes ten measurements of blood pressure over 10 min and then, via a self-contained modem, autodials a hospital-based computer, and downloads its memorized data trans-telephonically.

Referring clinicians preset a 'level of alert' for high blood pressure which, by default, is set to 165/105 mmHg without proteinuria, or 155/100 mmHg with proteinuria. High pressure readings automatically trigger a special signal on a radio-pager carried by a member of the research team, who used a portable computer remotely to log into the hospital-based computer. Thus a rapid medical or midwifery response to system recognition of any significant hypertension can be guaranteed. In such circumstances, hypertensive women could be telephoned immediately and asked to repeat their pressure measurement after 30 min rest. If the pressure was still high, hospital admission could then be arranged.

Referral into the study

Over a period of a year, obstetricians or midwives referred women who, at routine antenatal checks in hospital or in the community, were found to have sufficiently high blood pressures as to warrant admission by conventional obstetric standards.

Following a full explanation of the study, women who agreed to participate were randomized into two groups using a spcially adapted computer software package which included stratification for obstetrician and parity. One group comprising 49 women were admitted to hospital for conventional blood pressure management (hospital group), and the second group comprising 50 women were allowed to go home with the Cambridge blood pressure telemetry system (home group). Only one woman refused to participate at this stage.

After entry into the trial, each woman's clinical care remained the responsibility of the referring obstetrician or primary health care team. If a woman had repeated episodes of hypertension, she remained in the management group to which she was allocated initially.

Women in the hospital group had blood pressure measurements taken every 4 h, using either a mercury sphygmomanometer or a Dinamap automated pressure recorder. Their subsequent care was conventionally managed by the hospital-based midwives and obstetricians.

Women in the home group were provided with the telemetry equipment installed by one of the clinical team members. (In a minority of cases, women took the equipment home and installed it themselves). Each woman was given an instruction booklet describing the system and its usage, and what to do in the event of difficulties. They were also given telephone numbers of the research team, so that immediate assistance could be summoned if needed. Each woman then carried out a 'dummy run' in the presence of one of the team to ensure that all instructions were understood.

Exit from the study

A referral episode was terminated whenever (i) women in the hospital group were returned home because the obstetrician considered their blood pressure to have 'settled'; (ii) women in the home group had five consecutive measurement sessions each with low average pressures, namely $<140/90$ mmHg without proteinuria, or $<135/85$ mmHg with proteinuria (each session included 10 individual readings); (iii) women in the home group had sufficiently high average pressures to warrant admission, usually $\geqslant 165/105$ mmHg without proteinuria, or $\geqslant 155/100$ mmHg with proteinuria; (iv) women were admitted to the delivery unit.

The anxiety measures

The Spielberger state-trait anxiety inventory (Spielberger *et al* 1970) is a well validated instrument used widely in research. It measures two components of anxiety. Trait anxiety is the relatively stable degree of underlying anxiety in the personality. State anxiety is more labile, and reactive to external stimuli.

Collection of socio-demographic and psychological data

Socio-demographic and psychological data were collected according to the following schedule. During the period of the study all women attending the Rosie antenatal clinic completed the Spielberger trait anxiety questionnaire at their routine 30-week antenatal visit to the clinic.

On recruitment they completed the Spielberger state anxiety questionnaire and the woman's management preference was noted.

At randomization the woman's reaction to allocation was assessed by one of the team (W.C.) on a scale ranging from 1 (very pleased) to 6 (very upset).

The first evening the woman completed the Spielberger state anxiety questionnaire and a self-report booklet was used to gather information on: previous health (particularly hypertension), emotional problems, attitude to hospital admission, and experience of using electronic equipment.

On the third evening and alternate evenings during the monitoring period the women completed the Spielberger state anxiety questionnaire.

After delivery the women completed a self-assessment of anxiety caused by the monitoring (i.e., within a week) on a scale ranging from 0 (no anxiety) to 10 (very anxious).

Response rates

During a period of a year 99 women were recruited for participation in the psychological section of the study, of whom 49 were randomized to be managed in hospital and 50 returned home. Four women refused to participate and four withdrew after initially participating. The remainder (91) were followed up by W.C. until 8 weeks after delivery. Six women in the home group transmitted high blood pressure recordings and were urgently admitted to hospital. As a result some of their anxiety measures were recorded both in hospital and at home, thus we excluded them from the analysis.

Finally, a group of 18 women were not included in the final data analysis for the following reasons: (i) insufficient written English to complete the questionnaires (one woman in each group); (ii) one diabetic woman in the home group who had an intrauterine death; (iii) one woman was unknowingly in labour

Table 1. Characteristics of the pregnant hypertensive women managed either in hospital or at home using blood pressure telemetry

Variable	Hospital group (n = 31)		Home group (n = 36)	
Age (years)	29·0	(4·3)	28·5	(4·7)
Number married/in stable relationships	31	(100%)	34	(98%)
Number in socio-economic groups I, II, IIINM	25	(81%)	27	(77%)
Number of primiparae	22	(71%)	20	(57%)
Blood pressure at referral (mmHg)				
Systolic	142	(13·1)	145·6	(10·0)
Diastolic	92·1	(6·7)	92·4	(5·6)
Gestation at referral (weeks)	35·7	(4·5)	37·1	(5·4)
Mean no. of referrals	1·3	(0·9)	1·4	(1·1)
Duration of monitoring (days)	4·9	(9·5)	4·6	(5·3)
Blood pressure during monitoring (mmHg)				
Systolic	126·6	(10·7)	137·5	(9·6)
Diastolic	77·2	(11·5)	74·1	(7·2)
Gestation at delivery (weeks)	39·9	(1·4)	39·7	(1·5)
Normal vaginal delivery	21	(68%)	19	(54%)
Birthweight (kg)	3·3	(0·5)	3·9	(1·5)

Results are mean (SD) or n (%) values as appropriate.
There were no significant differences for any of the variables between the two groups using Student's t or χ^2 tests as appropriate.

when she was randomized to the hospital group; (iv) 14 women failed to complete their anxiety questionnaires adequately or did not return them (10 in the hospital group and four in the home group).

Data sets from 67 women were used (31 in the hospital group and 36 in the home group).

The women who failed either to complete or return the questionnaires were compared with the group of respondents in terms of their socio-demographic and psychological characteristics.

Data analysis

Results were analyzed using the Statistical Package for the Social Sciences (SPSS Inc.) Student's t test, and the χ^2 test were used where appropriate.

Results

We found no significant differences between the 67 responders and the 14 non-responders in terms of parity, marital status, age, anxiety levels before randomization, and blood pressure and gestational age at referral. (Full results are not provided here).

Only 43 women were still being monitored by the third evening after their first admission: the remainder had either been delivered, or their pressures had settled and so monitoring was stopped. By the fifth evening only ten women required monitoring.

Obstetric and socio-economic characteristics

We found no significant differences between the hospital and home groups in terms of maternal age, parity, marital status, socio-economic status. Similarly, there were no significant differences between the two groups in terms of gestational age or pressure measurements at referral, in the number of monitoring episodes, in total duration of monitoring, in average pressure during monitoring, in gestational age at delivery, in mode of delivery or in birthweight (Table 1).

Anxiety measures

Objective measures. We found no significant difference between the two groups in terms of their anxiety levels at 30 weeks (trait anxiety) or at the time of recognition of their hypertension (state anxiety). These findings are to be expected, as both measures were taken before the women were randomized for management at home or in hospital (Table 2). We also failed to demonstrate any significant difference in anxiety between the home and hospital groups either on the first evening during monitoring, or on the third evening. This was so, even though both groups of women had increased anxiety when their hypertension was diagnosed, and both showed a similar decline to normal levels by the third evening.

Self-assessment measure. There was no significant difference between the two groups in the women's perceptions of how anxious they had been during the period of monitoring (as measured on a self-administered analogue scale which ranged from 0 (not at all anxious) to 10 (extremely anxious). The hospital group rated 4·1 (2·0) and the home group 2·7 (2·8) (t = 1·86, P<0·07).

Previous experience of hospital or of electronic equipment

Although full results are not given here, we found no significant relation between any of the clinical, socio-demographic or

Table 2. Spielberger trait and state anxiety in hypertensive pregnant women managed either in hospital or at home using blood pressure telemetry

	Hospital group			Home group				
	n	mean	(SD)	n	mean	(SD)	t	P
Trait anxiety at 30 weeks	24	33·1	(9·1)	29	34·5	(8·1)	−0·58	0·563
State anxiety								
At randomization	31	38·5	(10·5)	36	39·7	(11·3)	−0·43	0·669
Evening of randomization	31	33·7	(9·3)	36	36·8	(8·4)	−1·42	0·160
Third evening	16	31·6	(7·5)	27	30·8	(8·6)	0·34	0·738
Fifth evening	2	29	(5·7)	8	27	(5·1)	0·48	0·692

psychological measures, admission to hospital prior to the current pregnancy, or familiarity with using electronic equipment at work or at home.

Preference for type of management

Before randomization, 51 of the 67 women (78%) had stated a clear preference for telemetric management at home. We found no difference between these women and the remaining women in terms of their clinical, socio-demographic or psychological measures.

Blood pressure and anxiety levels

We found no significant correlation between blood pressure and anxiety levels, either at 30 weeks, at the time of diagnosis of the hypertension, on the first evening during monitoring, or on the third evening. Our findings were similar whether the pressure was measured at home or in hospital.

Discussion

When we set out to compare anxiety in hypertensive pregnant women we had anticipated that women managed in hospital would have significantly higher anxiety levels than those managed telemetrically from home. Clearly we have been unable to demonstrate this. If anything, women were slightly more anxious at home at first, though the difference was not statistically significant. By the end of the third day of intermittent pressure monitoring, anxiety levels had decreased considerably, and indeed they were almost identical in the two groups.

We have reported previously that normotensive pregnant women were confident about using our telemetry equipment at home. In the present study, too, the home group reported themselves to be reasonably confident about using our equipment, and they had no particular difficulties in transmitting their results. However, it is likely that being diagnosed as hypertensive, followed by having to cope with the problem at home, was initially quite stressful—particularly with the possibility of admission looming. Following such stressful events, Janis (1958) has indicated an increased need for approval and support from authority figures. The women admitted to hospital may have been less anxious than the women at home because they had reassurance and support from hospital staff and fellow-patients. The anxiety of the women at home might have been reduced if they had had contact with a doctor or midwife immediately after the first 'solo' measurement session, but such support was not included in our protocol.

Patient compliance was not a particular problem in this study, as only 10 of the hospital group and four of the home group failed to complete or return their questionnaires. We had expected that many more women would default. Perhaps the lower compliance in the hospital group was due to their disappointment at being admitted, but the difference was not statistically significant.

We have previously established that telemetric management of hypertension in pregnancy enables women to avoid hospital admission. The present study shows that telemetric monitoring in the community is not associated with any greater or lesser anxiety than is conventional monitoring in hospital.

Acknowledgments

This study was funded by the Health Promotion Research Trust and approved by the local ethics committee.

References

Budd K. (1977) Behavioral tasks of the high risk maternity patient In *Nursing of Women in the Age of Liberation* (Lytle N. A., ed.) Dubuque, Iowa, pp. 125-141.

Dalton K. J., Manning K., Robarts P. J, Dripps J. H. & Currie J. R. (1987) Computerized home telemetry of maternal blood pressure in hypertensive pregnancy. *Int J Biomed Comput* **21**, 175-187.

Department of Health (1989) *Report on Confidential Enquiries into Maternal Deaths in England and Wales 1982–84*, Her Majesty's Stationery Office, London.

Hugh-Jones P., Tanser A. R. & Whitby C. (1964) Patients view of admission to a London teaching hospital. *Br Med J* **2**, 660-664.

Janis I L. (1958) *Psychological Stress*, John Wiley, New York, p 158.

Mason J W., Sachar E. J., Fishman J. R., Hamburg D. A. & Handlon J. H. (1965) Corticol responses to hospital admission. *Arch Gen Psych* **13 (1)**, 1-8.

Merkatz R. (1978) Prolonged hospitalization of pregnant women: the effects on the family. *Birth Fam J* **5 (4)**, 204-206

Mooney P. J., Dalton K. J., Swindells H., Rushant S., Cartwright W. J. & Juett D. (1991) Blood pressure measured telemetrically from home throughout pregnancy *Am J Obstet Gynecol* **163**, 30-36

Redman C. (1989) Eclampsia still kills *Br Med J* **296**, 6631, 1209-1210

Rubin R. (1975) Maternal tasks in pregnancy. *Matern Child Nurs J* **4**, 143-153.

Spielberger C. D., Gorsuch R. L. & Lushene R. E. (1970) In *Manual for the State-Trait Anxiety Inventory* Consulting Psychologists Press, Palo Alto, CA

SPSS/PC Plus (Norusis M. J., ed), SPSS Inc., Chicago, Illinois.

Swindells H. S., Mooney P., Cartwright W. J. & Dalton K. J. (1990) Blood pressure telemetry from home. *Midwife, Health Visitor & Community Nurse* **26 (3)**, 88-90.

Volicer B J & Volicer L. (1978) Cardiovascular changes associated with hospitalization. *J Psychosom Res* **22**, 159-168

Volicer B. J. (1978) Hospital stress and patient reports of pain and physical status *J Hum Stress* **4 (2)**, 28-37.

White M. & Ritchie J. (1984) Psychological stressors in antepartum hospitalization· Reports from pregnant women. *Matern Child Nurs J* **13**, 47-56.

Wilson-Barnett J. (1978) *Stress in Hospital*, Churchill Livingstone.

Received 25 January 1991
Accepted 19 November 1991

British Journal of Obstetrics and Gynaecology
March 1992, Vol 99, pp. 186–189

OBSTETRICS

The accuracy of catheter-tip pressure transducers for the measurement of intrauterine pressure in labour

S. CHUA
Lecturer

S. ARULKUMARAN
Associate Professor

M. YANG
Senior Resident

S. S. RATNAM
Professor and Head of Department

Department of Obstetrics & Gynaecology, National University Hospital, Lower Kent Ridge Hospital, Singapore 0511

P. J. STEER
Professor and Head of Department

Department of Obstetrics & Gynaecology, Charing Cross and Westminster Medical School, West London Hospital, Hammersmith Road, London W6 7DQ

ABSTRACT

Objective To assess the reliability of intrauterine pressure measurements in labour with transducer tipped catheters.

Design Prospective clinical study.

Setting Delivery ward, National University Hospital, Singapore.

Subjects 20 women admitted in early labour were randomly allocated to two groups.

Interventions Women in the first group had two catheters that had been tied together introduced transcervically into the same amniotic fluid pocket. The second group had two catheters introduced in different directions so that each catheter tip was in a different pocket of amniotic fluid.

Main outcome measure The contraction to contraction pressure difference recorded by the two catheters in the same uterus. In addition, the cumulative uterine active pressure generated by one catheter was compared with that of the other.

Results There were differences in peak pressure of up to 4–5·3 kPa (30–40 mmHg) during some contractions. The difference in pressure recordings between the two catheters could not be explained by effects of loculation of amniotic fluid. However, the pressures recorded were not systematically higher in one catheter than in the other. Cumulative uterine activity was very similar when assessed by each catheter in the same uterus.

Conclusion Intrauterine pressure measurements using transducer tipped catheters provide reliable information on the cumulative pressure wherever the catheter tip was sited in the uterus, but there are variations in pressures recorded during individual contractions.

The measurement of intrauterine pressure first became practical in routine clinical practice when Williams & Stallworthy (1952) developed an intrauterine pressure catheter which could be passed into the uterus transcervically. Since then, intrauterine pressure catheters have generally been accepted as a reliable means of providing accurate information on intrauterine activity. However, Knoke *et al.* (1976) described a series of experiments in which three intrauterine catheters were passed simultaneously into the same uterus during labour. They showed large differences between the three readings obtained on a contraction by contraction basis. Their findings and other anecdotal reports have given rise to doubts as to whether intrauterine pressure measurement is a valid way of assessing uterine activity in labour (Goodlin 1989, 1990).

The objective of this study was to assess the accuracy of intrauterine pressure measurements by comparing two simultaneous recordings. The variation of intrauterine pressure when catheter-tip intrauterine pressure transducers were inserted in the same pocket of amniotic fluid in the uterine cavity was compared with the variation when they were inserted in random locations within the uterine cavity.

Correspondence: S. Chua.

Subjects and methods

Twenty women admitted to the National University Hospital, Singapore, in the early active phase of labour with ruptured membranes were recruited for the study. Informed consent was obtained. The women were randomly assigned to two groups, using a random number table. It was decided to study 10 in each group on an empirical basis as it was considered that if major differences were not found with this number (20 in total) then any differences which might be apparent with larger numbers would be sufficiently rare as to be clinically unimportant. The catheters were calibrated before use according to instructions set out in the Sonicaid handbook. They were inserted transcervically. The accuracy of each pair of catheters was checked before insertion by simultaneous insertion to equal depths in sterile fluid; the reading from the second catheter was recorded when the first catheter read 0·0, 1·3, 2·7, 4·0, 5·3 and 6·7 kPa (0, 10, 20, 30, 40 and 50 mmHg). The calibration checks showed that the discrepancies between the catheters were: <0·1 kPa (1 mmHg) 30%, 0·1 kPa (1 mmHg) 23%, 0·3 kPa (2 mmHg) 17%, 0·4 kPa (3 mmHg) 17%, 0·5 kPa (4 mmHg) 10% and 0·8 kPa (6 mmHg) 3% (i.e., the difference was ≤0 5 kPa (4 mmHg) on 97% of occasions). The

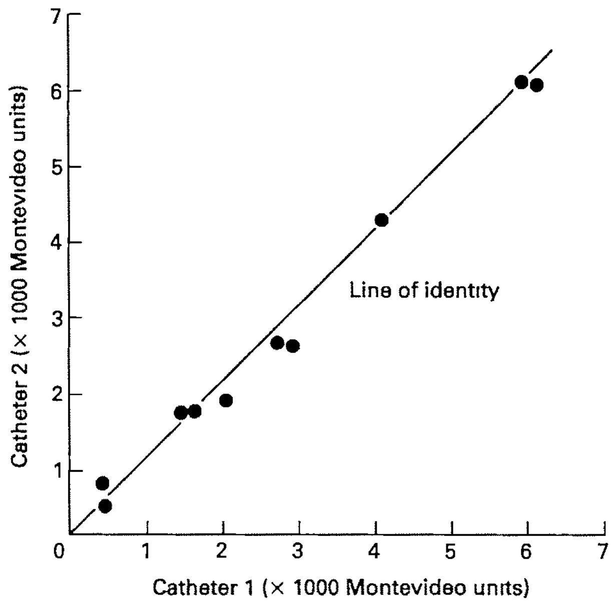


Fig. 1. Comparison of the sum of active pressures recorded by each of two catheters inserted independently in the same uterus in 10 women in labour.

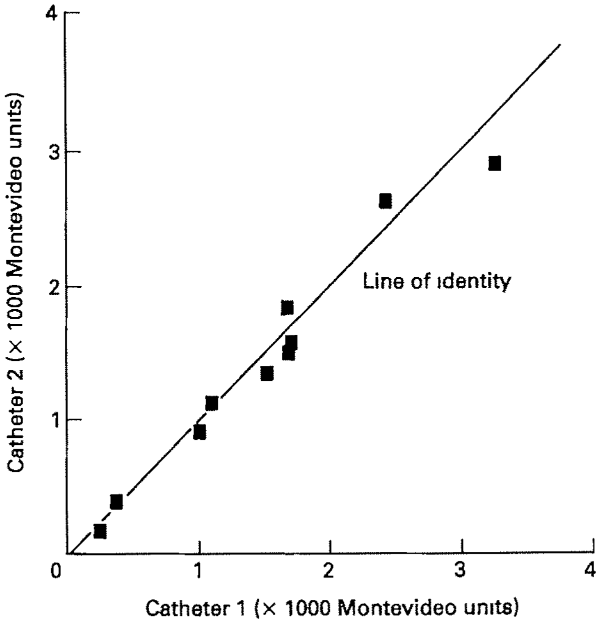


Fig. 2. Comparison of the sum of active pressures recorded by two catheters tied together before insertion in the uterus in 10 women in labour.

women in group 1 had two sterile Gaeltec catheter-tip pressure transducers inserted independently into the same uterus. One catheter was inserted posteriorly behind the fetal head, and the other catheter anteriorly in front of the fetal head. In group 2, the two catheters were tied together with sterile catgut before insertion, so that the tips of both catheters were at all times less than 1 cm apart, and presumably in the same fluid compartment in the uterus after insertion.

For every set of observations, one catheter of each pair was connected to a Sonicaid FM3R fetal monitor and the other catheter was connected to a Sonicaid FM6 fetal monitor. The baseline pressure in both catheters was set to an identical level by the manual facility available in the FM3R fetal monitor. The peak pressures were recorded from the two catheters for successive contractions in the 10 women in each group. The catheters were removed only when the women started bearing down in the early second stage of labour. The catheters that were tied together were checked on removal and showed no displacement from each other.

In each woman, the mean difference recorded by each catheter was compared using paired t-tests. The sum of active pressures recorded in each catheter was compared using the correlation coefficient (Figs. 1 & 2).

Results

There was no statistically significant difference in the mean age, gravidity and period of gestation between the two groups of women.

The results in each of the 20 women are summarized in

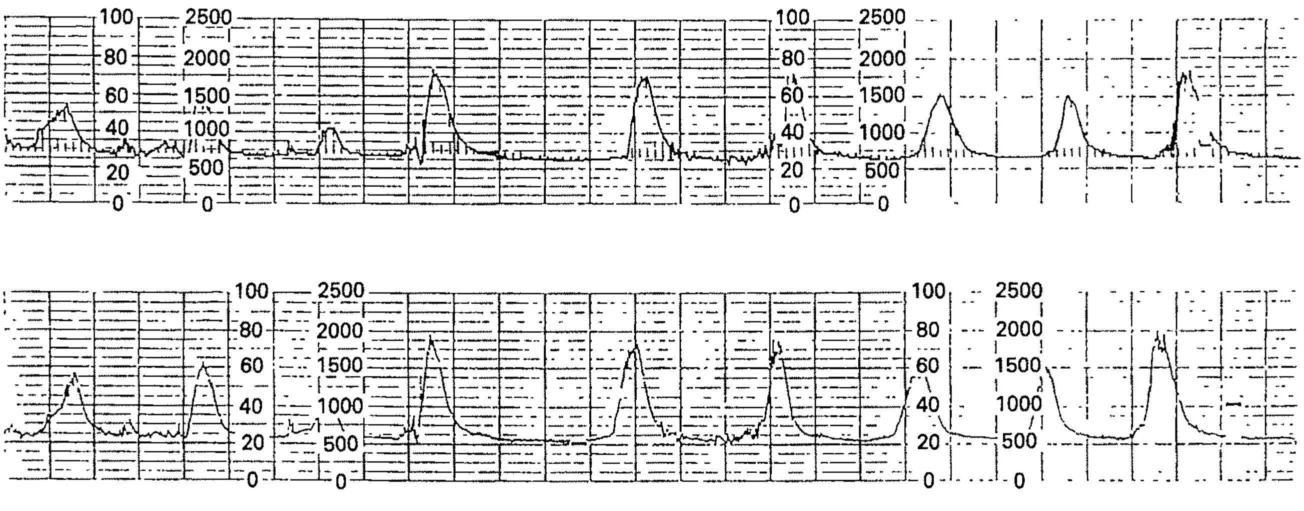


Fig. 3 Similar configuration of the contraction profiles in the two catheters.

Table 1. Differences in intrauterine pressure measurements recorded by two Gaeltec catheters inserted independently within the same uterus

Subject	*n*	Mean A (kPa)	Mean B (kPa)	Difference (kPa) Mean (SD)	*t*	*P*	Max diff (kPa)
1	94	8·62	8·63	0·01 (0·73)	0·13	0·90	1·6
2	96	3·80	3·62	0·24 (0·77)	3·04	0·03	4·0
3	59	6·52	5·54	0·98 (1·21)	6·23	<0·01	5·3
4	135	6·19	5·84	0·35 (0·51)	7·95	<0·01	2·7
5	82	6·96	6·85	0·12 (1·07)	0·98	0·33	4·0
6	41	4·97	5·33	0·36 (0·65)	3·57	<0·01	2·3
7	33	6·75	6·56	0·19 (0·71)	1·53	0·14	2·0
8	16	3·73	3·36	0·37 (0·58)	2·51	0·02	2·0
9	49	5·75	4·82	0·91 (1·08)	6·03	<0·01	3·5
10	18	5·12	3·33	1·79 (0·78)	9·74	<0·01	3·3

n = number of recorded measurements.

Tables 1 and 2. Although the recordings showed large contraction by contraction differences, with maximum differences of up to 5·3 kPa (40 mmHg) in group 1 and up to 4·0 kPa (30 mmHg) in group 2, the average mean difference in the active contraction pressure recorded between the two catheters was only 0·53 kPa (4·0 mmHg) and 0·52 kPa (3·9 mmHg) respectively. Set against mean active pressures of 5·6 kPa (42 mmHg) and 5·3 kPa (40 mmHg) in groups 1 and 2 respectively, the average differences were not clinically significant. This is reflected in the fact that the overall cumulative uterine activity was very similar. Figures 1 and 2 show that when the sum of active pressures recorded in each catheter are compared in each of the 20 women, there is little systematic difference in the recordings of intrauterine pressure. The differences in measurements between the two catheters were not affected by, or related to, the magnitude of pressures assessed. The configuration of the contraction profiles recorded in both catheters was very similar, even when peak contraction pressures varied between them (Fig. 3).

Discussion

The advantages of intrauterine pressure measurements over external cardiotocography, especially in restless or obese women, and those with abnormal progress of labour, have been reported (Csapo *et al.* 1970; Caldeyro *et al.* 1950; Lacroix 1968). But questions have been raised recently concerning the validity of intrauterine pressure measurements and quantification of uterine activity in labour once membranes have ruptured (Goodlin 1989, 1990).

Knoke *et al.* (1976) recorded intrauterine pressure with three fluid-filled intrauterine catheters (FFIUC) simultaneously in each of nine women in labour. Their conclusions were that the variation in recorded pressure likely to occur by chance due to the random nature of catheter placement and loculation of amniotic fluid was approximately 0·7–1·3 kPa (5–10 mmHg). They found a 25% measurement uncertainty and concluded that the pressure of one contraction measured with one catheter should not be given too much significance. However, they found the discrepancies in measured pressure were not systematic, and therefore over a period of several hours gross measurements of total uterine activity were comparable with all three catheters.

Steer *et al.* (1978) compared the measurement of intrauterine pressure using FFIUC with that measured using the Sonicaid-Gaeltec catheter-tip pressure transducer in four women. They showed only slight differences between the two methods. The small systematic under-reading of uterine pressures by the FFIUC was attributed to blockage in the fluid filled catheters. Neuman *et al.* (1972) compared pressures derived from fluid-filled catheters with those from an intrauterine sensor and found a coefficient of variation similar to that reported by Steer *et al.* (1978).

Our results confirm that while there may be contraction by contraction differences in recordings of intrauterine pressures from two catheter-tip pressure transducers in the same uterus, overall, there is little systematic difference.

Table 2. Differences in intrauterine pressure measurements recorded by two Gaeltec catheters tied together before insertion

Subject	*n*	Mean A (kPa)	Mean B (kPa)	Difference (kPa) Mean (SD)	*t*	*P*	Max diff (kPa)
1	18	8·44	8·14	0·26 (1·21)	0·93	0·37	3·7
2	45	7·17	7·58	0·41 (0·31)	3·83	<0·01	1·7
3	15	2·76	3·00	0·25 (0·43)	2·26	0·04	1·1
4	36	3·57	3·35	0·22 (0·68)	1·93	0·61	1·9
5	46	4·93	5·35	0·42 (0·54)	5·28	<0·01	2·0
6	33	6·91	6·16	0·75 (0·91)	4·69	<0·0	4·0
7	5	5·47	4·88	1·09 (0·49)	4·95	<0·01	1·7
8	36	5·53	4·90	0·63 (0·52)	7·29	<0·01	2·0
9	50	4·52	3·99	0·51 (0·60)	6·20	<0·01	1·7
10	82	5·35	4·70	0·65 (0·45)	13·23	<0·01	3·1

n = number of recorded measurements.

The observed measurement differences between intrauterine pressure transducers and the FFIUC obtained by Neuman *et al.* (1972) and Steer *et al.* (1978) were explained by the inherent inaccuracy of FFIUCs due to blockage and compression. However, this reasoning has to be revised because of the persistent differences in pressure recordings obtained when two catheter-tip pressure transducers were inserted independently into the same uterus (Table 1).

It is tempting to suppose that persistent differences in measured active pressure in two catheters placed in the same uterus are due to loculation of fluid within this uterus, so that different compartments develop different active pressures during the same contraction. However, the persistent difference in peak active pressures obtained when two catheters are tied together (and hence in the same pocket of amniotic fluid (Table 2) demonstrates that this is not likely to be the explanation. The reasons for the individual variations from contraction to contraction remain obscure, but may be due to mechanical (direct force) rather than fluid pressure acting on the transducers. Our findings show that although there are variations in the measurement of intrauterine pressure from contraction to contraction, systematically, these variations are probably of little clinical significance. Thus, intrauterine pressure measurements using transducer tipped Gaeltec catheters provide reliable long-term information on uterine activity wherever the catheter tip was sited in the uterus as shown by cumulative pressure in any one labour.

References

Caldeyro R., Alvarez H. & Reynods S. R. M. (1950) A better understanding of uterine contractility through simultaneous recording with and internal and a seven channel external method. *Surg Gynecol Obstet* **91,** 641-650.

Csapo A. (1970) The diagnostic significance of the intrauterine pressure. *Obstet Gynecol Surv* **25,** 403-435.

Goodlin R. C. (1989) Postpartum uterine activity: Evaluation of an intrauterine pressure transducer. (Letter) *Obstet Gynecol* **74,** 283-284.

Goodlin R. C. (1990) Uterine activity during spontaneous labour after previous lower-segment caesarean section (Letter). *Br J Obstet Gynaecol* **97,** 277-279

Lacroix G (1968) Monitoring labour by an external tokodynamometer. *Am J Obstet Gynecol* **101,** 111-119.

Knoke J D , Tsao L L., Neuman M. R. & Roux J. F. (1976) The accuracy of intrauterine pressure during labour; a statistical analysis. *Comp Biomed Res* **9,** 177-186.

Neuman M R., Jordan J. A., Roux J. F. & Knoke J. D. (1972) Validity of intrauterine pressure measurements with transcervical intra-amniotic catheters and an intrauterine miniature pressure transducer during labour. *Gynecol Invest* **3,** 165-175.

Steer P J., Carter M. C., Gordon A. J. & Beard R. W. (1978) The use of catheter-tip pressure transducers for measurement of intrauterine pressure in labour. *Br J Obstet Gynaecol* **85,** 561-566.

Williams E. A. & Stallworthy J. A. (1952) A simple method of internal tocography. *Lancet* **i,** 330-332.

Received 29 November 1990
Accepted 24 September 1991

British Journal of Obstetrics and Gynaecology
March 1992, Vol. 99, pp. 190–196

OBSTETRICS

Prenatal microbiological risk factors associated with preterm birth

H. M. McDONALD
Chief Microbiologist
J. A. O'LOUGHLIN
Senior Visiting Specialist
P. JOLLEY
Microbiologist
R. VIGNESWARAN
Senior Visiting Specialist
Adelaide Medical Centre for Women and Children
Queen Victoria Hospital
Adelaide, Australia
P. J. McDONALD
Professor, Microbiology and Infectious Diseases
Flinders University
Adelaide, Australia

ABSTRACT

Objective To study the vaginal flora of pregnant women at 22–28 weeks gestation to determine whether the presence of specific micro-organisms is significantly associated with preterm birth and prelabour rupture of the membranes.

Design A comprehensive descriptive prospective study of the vaginal micro-flora of women between 22–28 weeks gestation comparing those who gave birth preterm (<37 weeks) with those who gave birth at term. Microbiological assessment included cultures for aerobic and anaerobic bacteria, yeasts, genital mycoplasmas and *Trichomonas vaginalis*. Multiple logistic regression analysis was used to account for confounding obstetric and demographic variables.

Setting The Queen Victoria Hospital, Adelaide, South Australia.

Subjects 135 women who gave birth preterm compared to 651 women who gave birth at term.

Main outcome measure Preterm birth and preterm prelabour rupture of membranes (PROM)

Results The prevalence of *Gardnerella vaginalis* between 22–28 weeks was significantly higher in women who gave birth preterm compared to women who gave birth at term (23% *vs* 15%; multiple logistic regression odds ratio (OR) 1·8, 95% confidence intervals (CI) 1·01–3·2, $P<0\cdot05$. *Ureaplasma urealyticum* was also found in a higher proportion of women who gave birth preterm (49% *vs* 32% OR 1·7, 95% CI 1·1–2·6, $P<0\cdot0005$). Preterm PROM occurred in 42% of whom 60% were carriers of *U. urealyticum* between 22–28 weeks, compared with 32% in the term group (OR 3·2, CI 1·7–6·1, $P<0\cdot0005$). When women who received antibiotics between the midtrimester swab and labour were excluded, *G. vaginalis* was also significantly associated with preterm PROM (OR 2·7, CI 1·1–6·5, $P<0\cdot05$). The presence of vaginal enteropharyngeal bacteria (*E. coli, Klebsiella* spp., *Haemophilus* spp., *Staph. aureus*) in the midtrimester was not predictive of preterm birth, but when these organisms were found in labour, they appeared to have been acquired later in the pregnancy.

Conclusion Women carrying *G. vaginalis* or *U. urealyticum* during the midtrimester had nearly twice the risk of preterm birth, while women positive for *U. urealyticum* had more than a threefold risk of preterm PROM.

Immaturity resulting from preterm birth is a major unresolved health problem which is responsible for 75% of neonatal morbidity and mortality, and generates significant health care costs. The aetiology of preterm labour is multifactorial. In approximately one third of cases causative factors such as cervical incompetence, polyhydramnios and twins can be identified. In the other two thirds the cause is indeterminate.

Sociodemographic factors such as race, nutrition, smoking, marital status and heavy alcohol intake have been shown to be associated with increased risk of preterm labour and preterm birth. Recently infection has emerged as a potential factor that may contribute directly or indirectly to preterm birth. A number of clinical studies have indicated that asymptomatic genital tract infection may play a significant role in preterm birth, with several studies showing significant associations between carriage of specific organisms and increased risk of preterm birth (Regan *et al* 1981; Gravett *et al.* 1986; Amstey & Steadman 1976). Laboratory studies have indicated that certain micro-organisms produce enzymes (phospholipases) that can generate prostaglandins from the arachidonic acid in fetal membranes. Furthermore some organisms stimulate production of cytokines from macrophages, enhancing prostaglandin activity. Both of these mechanisms have the potential to initiate labour.

At the Queen Victoria Hospital we have been studying all preterm births since October 1986 and our study cohort to April 1990 comprises over 2500 women including 495 spontaneous preterm births. The first analysis and report of this cohort indicated that there were two distinct bacterial groups

Correspondence: Mrs H. M. McDonald, Microbiology Department, Queen Victoria Hospital, 160 Fullarton Road, Rose Park, Adelaide, Australia 5067.

isolated in the vagina that were strongly associated with preterm birth, namely a bacterial vaginosis group, and a second group we have described as enteropharyngeal, because of their prevalence in pharyngeal and enteric sites (McDonald *et al* 1991).

To determine whether these organisms were present earlier in pregnancy, we have studied prospectively the vaginal microflora during the second trimester of pregnancy and again in labour.

Subjects and methods

In an observational prospective study at the Queen Victoria Hospital between October 1986 and February 1990, the vaginal flora of women attending the antenatal clinic was sampled during the second trimester (22–28 weeks gestation) and again on admission to the hospital in labour. Women with complications which dictated preterm delivery by induction of labour or caesarean section, women with abdominal surgery during pregnancy and GIFT pregnancies were excluded from the analysis. The Queen Victoria Hospital is a tertiary obstetric referral hospital, of the 3000–3500 women delivered per year 60% are uninsured hospital service patients, the remainder have private insurance. Approximately one tenth of the total births are non-booked transfers from other health care institutions In this prospective study, only booked hospital service patients who were attending the antenatal clinic were enrolled. This study group formed part of the larger population used in our previous analysis of women in labour (in which both transfers from other hospitals and privately insured women were included). Both studies were performed concurrently.

In designing the study we were mindful of the large numbers of women who were expected to proceed to full-term (i.e., 92% of our study population). In order to limit the very time-consuming and costly work involved in recording data from all the women who gave birth at term, and although we had already performed the microbiological cultures on their midtrimester swabs, we planned to analyse the results of only one quarter of these women. The criteria used for enrolment into the comparison term group was the booking allocation to one of the four obstetric units of the hospital, under the control of one of the authors. The unit allocation process occurs at the booking visit and is randomized, and therefore not biased by geographical or other considerations.

Three swabs were taken from the posterior vaginal fornix using a speculum with a non-bacteriostatic lubricant. These swabs were cultured for all aerobes, genital mycoplasmas and anaerobes according to the methods described by McDonald *et al.* (1991). The isolation of *Gardnerella vaginalis* was based on a non-selective human blood plate so that only women with moderate to heavy growth of *G. vaginalis* would be detected. We considered moderate/heavy growth of *G. vaginalis* represented an imbalance of vaginal flora, whereas small numbers of *G vaginalis* may be present in normal vaginal flora together with lactobacilli. Tests for detection of *Chlamydia trachomatis* were not performed as the prevalence of this organism in our antenatal population group was known to be less than 1%. Placental culture was performed using a subamniotic swabbing technique. Histopathological examination of preterm placentas from women with suspected chorioamnionitis was performed. Data recorded included all associated obstetric factors known to place a woman at risk of preterm labour or preterm prelabour rupture of membranes (preterm PROM) such as multiple pregnancy, previous spontaneous preterm delivery, previous mid-trimester miscarriage or abortion, cervical incompetence, polyhydramnios, pyelonephritis, uterine malformations, or placenta praevia after 22 weeks with bleeding. Also recorded were maternal age, gravidity, parity, gestational age at delivery (determined by combination of last menstrual period and first or second trimester ultrasonography), preterm PROM, tocolytic therapy, birthweight, neonatal clinical assessment, laboratory investigations, placental histopathology and microbiology. Social class, a potential confounding variable, was not assessed, however, study participants were all hospital service patients, not privately insured.

Pregnancy outcomes measured were preterm birth (before 37 completed weeks gestation) and preterm PROM. Women delivered after 37 weeks gestation were defined to have been delivered at term. Only preterm birth was used as an outcome measure and not preterm labour without eventual preterm birth, as it is not always possible to differentiate this condition from false labour.

Statistical analysis

Univariate comparisons of proportions were made using the χ^2 test with Yates' correction for small numbers. Multivariate

Table 1. Demographic characteristics of the women in the study

	Preterm (n = 135)	Term (n = 651)	Odds ratio	95% CI	*P* value
Maternal age (years)	25·9 (6·0)	26·4 (5·3)			0·15 (*t* test)
Gestation (weeks)	34·2 (2·4)	39·5 (1·1)			
Birthweight (g)*	2339 (572)	3365 (450)			
Parity					
0	72 (53%)	312 (48%)			
1	38 (28%)	206 (32%)			
2	13 (10%)	94 (14%)			
3	12 (9%)	39 (6%)			0·2 (χ^2, 3 df)
Cigarette smoking	63/132 (48%)	235/616 (38%)	[2·5]	[0·6–10·6]	0·055
Substance abuse	2/132 (1·5%)	7/616 (1%)	[1·3]	[0·2–7·3]	ns

*excluding multiple pregnancy ns = not significant.

Results are mean (SD) values or number (%) as appropriate. Figures in square brackets denote values after multiple logistic regression analysis.

Table 2. Obstetric risk factors predisposing to preterm labour

	Preterm (*n* = 135) *n* (%)	Term (*n* = 651) *n* (%)	Odds ratio	95% CI	*P* value
Previous preterm delivery (>20 weeks)	23 (17)	25 (4)	5·1	2·8–9·4	<0·0005
Previous midtrimester miscarriage	7 (5)	14 (2)	2·5	0·98–6·3	<0·10
Multiple pregnancy	13 (10)	6 (1)	11·5	4·3–30·7	<0·0005
Cervical incompetence	4 (3)	1 (<1)			<0·005
Polyhydramnios (ultrasound confirmed)	3 (2)	2 (<1)			<0·10
Uterine malformation	0 (0)	3 (<1)			ns
Pyelonephritis during pregnancy	0 (0)	2 (<1)			ns

ns = not significant.

logistic regression analysis was performed using the GLIM statistical software programme, to allow for confounding demographic and obstetric variables. Odds ratios and 95% confidence intervals were calculated. A model using all factors thought to be associated with preterm labour and all organism groups was used in the regression analysis. Women with placenta praevia were excluded in the multiple logistic regression analysis.

This study was approved by the QVH ethics committee, and participating women gave informed consent.

Results

Between October 4, 1986 and December 31, 1988, a total of 534 women attending one of the four antenatal clinics (under the direction of one of the authors) had vaginal swabs between 22 and 28 weeks gestation. Between January 1, 1989 and February 14, 1990, after the study had been expanded to include women attending all four antenatal clinics, 1656 were sampled. A total of 2190 women were sampled from a population of 2570 (85%) women attending the clinics as specified. Those not sampled were excluded because they booked late in pregnancy (i.e., after 28 weeks), were irregular attenders, or refused consent. Of these 2190 women enrolled in the study, 135 gave birth spontaneously before 37 weeks gestation. The vaginal flora of this preterm group was compared to the vaginal flora of the control group of 651 women who proceeded to term.

The women in the term control group had similar demographic characteristics to those in the preterm group, including maternal age, gravidity, parity (Table 1). A higher proportion of women in the preterm group were cigarette smokers although this did not quite reach the 5% level of significance (48% *vs* 38%, $P = 0{\cdot}055$).

In the preterm group 44 of the 135 women (33%) had one or more obstetric risk factors, compared with 48 of 651 (7%) in the term group ($P<0{\cdot}0001$). As would be anticipated, previous preterm delivery, multiple pregnancy, and cervical incompetence were significantly more common in the preterm group (Table 2).

Overall, 160 of the 786 women (20%), including 26 in the preterm group, received antibiotics between the second trimester swabs and labour (12% for yeast infection, 1% for bacterial vaginosis, and 2% for urinary tract infection).

Multiple logistic regression analysis was performed to take account of these demographic and obstetric variables. Women with cervical incompetence, polyhydramnios, uterine malformation or pyelonephritis were excluded in the regression analysis due to the very low numbers observed.

In the univariate analysis, significant associations were demonstrated between the carriage of *G. vaginalis* and *U. urealyticum* during the second trimester and subsequent preterm birth. *G. vaginalis* was found during the second trimester in 23% of the preterm group compared with 15% of the term group, whereas *U. urealyticum* was detected in 49% compared with 32%, respectively (Table 3). These associations remained statistically significant after multiple logistic regression analysis (*G. vaginalis* $P<0{\cdot}05$; *U. urealyticum* $P = 0{\cdot}0005$). When women who had received antibiotics between the second trimester swab and labour were excluded, *G. vaginalis* and *U. urealyticum* remained significantly associated with preterm birth (*G. vaginalis* OR 2·0, 95% CI 1·0–3·9, $P<0{\cdot}05$; *U. urealyticum* OR 1·9, 95% CI 1·2–3·2: $P<0{\cdot}001$).

No significant associations were demonstrated between prenatal carriage of other aerobes, anaerobes, yeast, group B streptococci or *M. hominis* and preterm birth. Thus *G. vaginalis* and *U. urealyticum* were the only organisms present during the second trimester which were associated with preterm birth in this study.

Women who gave birth preterm were divided into two groups—those with preterm PROM, and those who laboured with intact membranes. The presence of *U urealyticum* in the second trimester was significantly associated with preterm PROM ($P<0{\cdot}0005$). Women carrying *U. urealyticum* had more than three times the risk of preterm PROM (OR 3·2) (Table 4). When women who received antibiotics after the second trimester swab were excluded *G. vaginalis* was also shown to be associated with preterm PROM (OR 2·7, 95% CI 1·1–6·5, $P<0{\cdot}05$). Preterm PROM was not associated with carriage of any other organism during the second trimester.

The acquisition and loss of organisms after the second trimester was determined by comparing the results of swabs taken on admission in labour, with those in the second trimester. Overall 71% of the preterm and term women shown in Table 3 were also successfully swabbed in early labour. 29% were not sampled due to a number of reasons, the most common being rapidity of labour. Our results indicated that when enteropharyngeal organisms (i.e., *E. coli*, *Klebsiella* spp, *Haemophilus* spp. and *Staph. aureus*) were found in labour, they were nearly all late acquisitions (84% in preterm group and 77% in term group) (Table 5). In contrast to this, only 30% of the bacterial vaginosis organisms *G. vaginalis* and *U. ure-*

Table 3. Midtrimester vaginal flora isolated from women with preterm birth compared with women delivered at term

Organism	Preterm (*n* = 135) *n* (%)	Term (*n* = 651) *n* (%)	Odds ratio	95% CI	*P* value
G vaginalis	31 (23)	97 (15)	1·9 [1·8] {1·7}	1·2–3·0 [1·01–3·2] {1·1–2·9}	<0·01 [<0·05] {<0·05}
U urealyticum	66 (49)	208 (32)	2·0 [1·7]	1·4–3·0 [1·1–2·6]	<0·0005 [<0·0005]
M hominis	11 (8)	38 (6)	1·7 [1·1]	0·9–3·5 [0·5–2·5]	ns [ns]
Bacteroides spp	47 (35)	190 (29)	1·4 [1·0]	0·9–2·1 [0·6–1·7]	ns [ns]
Peptostreptococcus spp	22 (16)	67 (10)	1·7 [1·3]	1·0–2·9 [0·7–2·5]	ns [ns]
Group B streptococci	14 (10)	71 (11)	1·1 [1·5]	0·6–2·0 [0·6–2·3]	ns [ns]
E coli	13 (10)	51 (8)	1·3 [1·5]	0·7–2·5 [0·6–2·3]	ns [ns]
Klebsiella spp	2 (1)	5 (1)	1·1 [1·9]	0·1–9·1 [0·2–17·6]	ns [ns]
Staph. aureus	8 (6)	44 (7)	1·0 [0·9]	0·4–2·1 [0·4–2·0]	ns [ns]
Haemophilus spp	1 (1)	0 (0)			ns
Yeast	23 (17)	114 (18)	1·0 [1·3]	0·6–1·7 [0·7–2·2]	ns [ns]

ns = not significant.
Figures in square brackets denote values after multiple logistic regression analysis.
Figures in { } brackets denote values after multiple logistic regression analysis using backwards elimination of variables to find the smallest adequate model.

alyticum isolated in labour were acquired late in pregnancy in the preterm group, the corresponding proportion was 40% in the term group.

Of the four variables that are significantly associated with preterm birth in this population, only two are potentially mutable after conception has occurred (colonization with *G. vaginalis* and colonization with *U. urealyticum*). Cigarette smoking might also be added to this last group although in our study this did not quite reach the 5% significance level. Using the prevalence of these exposures in our population, we have calculated the separate risks attributable to previous preterm delivery and multiple pregnancy as 13% and 8% respectively; 9% may be explained by colonization with *G vaginalis* and 24% by colonization with *U urealyticum*. The combined effect of all four factors gives a joint attributable risk of 48% i.e., 48% of preterm births may be explained by one or more of these factors. The joint risk attributable to *G vaginalis* and *U urealyticum*, after allowing for the effects of previous preterm birth and multiple pregnancy, is 26% (Breslow & Day 1980). The *G. vaginalis* and *U urealyticum* attributable risks are not independent, as 7% of women were colonized with both micro-organisms. Tests of independence show that women who are colonized with *G vaginalis* are more likely to also be colonized with *U. urealyticum* (OR 1·6, 95% CI 1·1–2·5, $P<0·05$).

Discussion

In this study we have shown that the vaginal carriage of *G vaginalis* and *U. urealyticum* during the second trimester is associated with an increased risk of preterm PROM and preterm birth. These associations remained valid after taking account of other obstetric and demographic variables namely age, gravidity, parity, drug abuse, smoking, multiple pregnancy and previous preterm delivery, and after excluding women who received antibiotics during the study. The presence of one or both of these organisms in the second trimester may therefore be considered predictive of preterm birth.

Our findings agree with those of Gravett *et al.* (1986) who in a prospective study sampled women at 32 weeks gestation and found associations between bacterial vaginosis, preterm PROM and preterm labour. *U. urealyticum* has previously been implicated as a cause of chronic amniotic fluid infection, and has been associated with stillbirths and preterm labour between 20 and 28 weeks gestation (Quinn 1988; Taylor-Robinson & McCormack 1980). The possible role of *U urealyticum* in preterm PROM has been highlighted by Gravett & Eschenbach (1986). Our findings confirm the role of *U. urealyticum* in preterm PROM.

Other prospective studies have failed to show similar associations. Minkoff *et al.* (1984) sampled women at their first antenatal visit and found no relation between bacterial vaginosis and preterm labour; they did, however, show an association between *U. urealyticum* and preterm labour, but not preterm delivery. Harrison (1986) cultured only for *U. urealyticum*, at the first visit and again between 32 and 38 weeks, however, he failed to find any link between its presence and low birthweight. More recently, Polk *et al.* (1989) in a study of 801 women at 22–30 weeks cultured for a wide range of aerobic

Table 4. Midtrimester vaginal flora isolated from women with preterm prelabour rupture of membranes (PPROM) compared with women delivered at term

Organism	PPROM (n = 57) n (%)	Term (n = 651) n (%)	Odds ratio	95% CI	P value
G. vaginalis	12 (21)	97 (15)	1·8 [1·8]	0·9–3·5 [0·8–4·0]	ns [ns]
U. urealyticum	34 (60)	208 (32)	3·1 [3·2]	1·7–5·5 [1·7–6·1]	<0·0005 [<0·0005]
M. hominis	4 (7)	38 (6)	1·5 [1·1]	0·5–4·3 [0·3–3·7]	ns [ns]
Bacteroides spp	18 (32)	190 (29)	1·1 [0·9]	0·6–2·1 [0·4–1·8]	ns [ns]
Peptostreptococcus spp	9 (16)	67 (10)	1·6 [1·4]	0·7–3·6 [0·6–3·4]	ns [ns]
Group B streptococci	5 (9)	71 (11)	0·9 [1·1]	0·3–2·3 [0·4–3·2]	ns [ns]
E. coli	3 (5)	51 (8)	0·7 [0·8]	0·2–2·5 [0·2–3·0]	ns [ns]
Klebsiella spp	2 (4)	5 (1)	2·6 [5·9]	0·3–22·2 [0·6–57·4]	ns [ns]
Staph. aureus	2 (4)	44 (7)	0·6 [0·5]	0·1–2·4 [0·1–2·4]	ns [ns]
Yeast	9 (16)	114 (18)	0·9 [1·4]	0·4–1·9 [0·6–3·3]	ns [ns]

ns = not significant.
Figures in square brackets denote values after multiple logistic regression analysis.

organisms plus the anaerobe *B. fragilis*. They found *M. hominis* and *C. trachomatis* to be significantly associated with preterm birth, but there was no such association with *G. vaginalis* or *U. urealyticum*. McGregor *et al.* (1990) in a small prospective study of 202 women at 20–28 weeks found an association between bacterial vaginosis and preterm labour (n = 33) but not preterm birth (n = 9).

A number of other studies have been published. Many have investigated only a single organism or a small group of organisms. Some contained too few subjects for meaningful analysis. In others, preterm labour rather than preterm birth has been used as an outcome measure, which in our view is unsatisfactory because of the difficulties associated with the definition of preterm labour and its differentiation from false labour states. Not all workers appear to have recognized the difficulties and complexities inherent in this type of study and the necessity of making appropriate adjustments to take account of confounding demographic and obstetric variables.

Our prospective study is larger than most previously reported and we have endeavoured to take into account known variables associated with preterm birth but, even so, it has limitations. As in other studies, the microbiologic status of each woman was classified on the results of a single culture and therefore small errors in classification are possible. We did not attempt to classify bacterial vaginosis status according to the direct specimen smear, but have considered the finding of a heavy growth of *G. vaginalis* as a marker. Whereas we have calculated the attributable risks for colonization with *G. vaginalis* and *U. urealyticum*, these must be interpreted with caution as this implies the relations are causal. This has yet to be determined.

Notwithstanding the afore mentioned limitations, we submit that we have demonstrated a link between *G. vaginalis* and preterm birth. This is supported by the results of our previous study which showed a significantly higher prevalence of *G. vaginalis* in women in preterm labour (McDonald *et al.* 1991).

Table 5. Changes in vaginal flora in late pregnancy in 93 women delivered preterm (PT) and 467 women delivered at term (T)

	No. of women with positive cultures in							
	Midtrimester		Labour		Midtrimester and labour		Late acquired (%)	
Organism	PT	T	PT	T	PT	T	PT	T
Bacterial vaginosis group								
G. vaginalis	24	65	10	25	7	13	30	48
U. urealyticum	42	150	40	151	28	93	30	38
Enteropharyngeal group (*E. coli*, *Klebsiella* spp., *Haemophilus* spp., *S. aureus*)	14	72	19	48	3	11	84	77

Recent reports have demonstrated the pathogenic potential of this organism as evidenced in its role in postpartum endometritis and pelvic inflammatory disease (Reimer & Reller 1984; Eschenbach *et al* 1988). To this, must now be added the growing body of evidence pointing to an association with preterm birth.

The second significant finding of this study is that a well defined group of enteropharyngeal organisms, previously shown to be associated at time of labour with preterm birth, is not generally present during the second trimester (McDonald *et al.* 1991). The presumption must be that these organisms were acquired later, before the start of labour. Although the prevalence of gram negative bacteria in the vagina is known to increase post partum, our studies (Table 5) and those of others (Goplerud *et al.* 1976) of the vaginal flora during normal pregnancy have shown a decrease in the last trimester. Indeed, in our study, 84% of preterm (and 77% of term) women found to be culture positive for these organisms in labour had been culture negative in the mid-trimester. Of the small number of enteropharyngeal organisms that were present in the midtrimester, 84% were transient and not subsequently found in labour. This supports the concept that enteropharyngeal organisms present at time of labour are usually recent acquisitions.

There are in our view, distinct and separate mechanisms through which the two groups of organisms might contribute to the initiation of preterm labour. The first is the group of women who harbour high numbers of bacteria that produce phospholipase. Women with bacterial vaginosis have numbers of *G. vaginalis* 100 times higher than in women without bacterial vaginosis Furthermore the numbers of anaerobes associated with bacterial vaginosis may be 1000 times greater (Spiegel *et al.* 1980). Laboratory studies have demonstrated that certain bacteria such as *G. vaginalis* and *U. urealyticum* produce high levels of phospholipase (Bejar *et al.* 1981; De Silva & Quinn 1986). Critical levels of phospholipase may be reached that might stimulate labour preterm by the release of bound arachidonic acid and so initiate a cascade of prostaglandins. It is, however, difficult to understand the role of *U. urealyticum* in preterm labour as it is so commonly isolated from the vagina (35% prevalence in our population group).

The second group is characterized by the acquisition of enteropharyngeal organisms. In general, these bacteria have virulence factors (e.g., anti-phagocytic capsules, endotoxin) that are capable of stimulating prostaglandin production by macrophages directly or through the release of several components of the cytokine network, namely tumour necrosis factor, interleukin 1 and platelet activating factor (Romero *et al.* 1989). In addition, infection with these organisms, unlike bacterial vaginosis, often stimulates a host response in which large numbers of macrophages are stimulated. We hypothesize that these virulent bacteria are introduced to the vagina and stimulate a local immune response of the type that is associated with containment of mucosal challenge and establishment of such bacteria as 'normal flora'. This process may be capable of stimulating labour.

For most preterm births there is no apparent cause. Comprehensive epidemiological data are available. Demographic studies have indicated that preterm birth is more common amongst non-Caucasians, women with lower socioeconomic status, the unmarried and the very young (Main 1988). Similarly, environmental associations such as ethanol consumption, cigarette smoking, poor nutrition and substance abuse have been identified. There now exists a large body of evidence supporting an infective role in the aetiology of preterm birth. Such infection, it is contended, is not always apparent and many cases of so-called idiopathic labour may have an underlying infective causation.

We would contend that it is possible, from demographic studies, to describe a profile of a woman at high or low risk of preterm birth. It is now also possible to describe a microbiological profile of a woman at increased risk of preterm birth. These demographic and microbiological high risk groups may be linked. Women in the high risk demographic group may have different behavioural characteristics to those in the low risk group. These behavioural patterns may affect the vaginal microbiological ecosystem. Variables such as hygiene may be a factor. The relation of coitus in pregnancy to preterm labour has been investigated with conflicting results, understandably, as such studies are fraught with difficulty. We believe, however, that there is a need for comprehensive studies into sexual behaviour in pregnancy. These studies should involve detailed sexual practices, sexual hygiene and multiplicity of partners.

If bacterial vaginosis or *G. vaginalis* is a predictor of preterm birth, the opportunity may exist for intervention leading to a reduction in the preterm birth rate. However, enteropharyngeal organisms if acquired late in the pregnancy, may present different problems, as how and why they might gain entry to the vagina would need to be determined if appropriate preventative strategems are to be contemplated.

Acknowledgments

We gratefully acknowledge the technical assistance provided by Ms E. Ribic, Mrs M. Alderman, and QVH Microbiology; the cooperation of the Medical and Nursing staff, the clerical assistance provided by Ms L. Smith; and special thanks to Dr Gary Glonek, Consultant in Statistics, Flinders University, South Australia.

This work was supported by grants from the Channel 10 Children's Medical Research Foundation and from the National Health and Medical Research Council of Australia.

References

Amstey M. S. & Steadman K. T. (1976) Asymptomatic gonnorrhoea and pregnancy. *J Am Vener Dis Assoc* **3**, 14-16.

Bejar R., Curbelo V., Davis C & Gluck L. (1981) Premature Labour II. Bacterial sources of phospholipase *Obstet Gynecol* **57**, 479-482

Breslow N. E & Day N E. (1980) Statistical methods in cancer research—Vol. 1. The analysis of case-control studies. IARC scientific publication no. 32. Lyon, IARC 73-78.

De Silva N & Quinn P. A. (1986) Endogenous activity of phospholipases A and C in *Ureaplasma urealyticum J Clin Microbiol* **23**, 354-359

Eschenbach D. A., Hillier S , Critchlow C., Stevens C., DeRouen T & Holmes K. K. (1988) Diagnosis and clinical manifestations of bacterial vaginosis. *Am J Obstet Gynecol* **158**, 819-828.

Goplerud C. P., Ohm M. J. & Galask R. P. (1976) Aerobic and anaerobic flora of the cervix during pregnancy and the puerperium. *Am J Obstet Gynecol* **126**, 858-868

Gravett M G., Nelson H. P., De Rouen T, Critchlow C. C , Eschenbach D. A. & Holmes K. K. (1986) Independent association of bacterial vaginosis and *Chlamydia trachomatis* infection with adverse pregnancy outcome. *JAMA* **256,** 1899-1903.

Gravett M. G. & Eschenbach D. A. (1986) Possible role of *Ureaplasma urealyticum* in preterm premature rupture of the fetal membranes. *Pediatr Infect Dis* **5,** S253-S257.

Harrison H. R. (1986) Cervical colonization with *Ureaplasma urealyticum* and pregnancy outcome: prospective studies. *Pediatr Infect Dis* **5,** S266-S269.

Main D. M. (1988) The epidemiology of preterm birth. *Clin Obstet Gynaecol* **31 (3),** 521-532.

McDonald H. M., O'Loughlin J. A., Jolley P., Vigneswaran R. & McDonald P. J. (1991) Vaginal infection and preterm labour. *Br J Obst Gyn* **98,** 427-435.

McGregor J. A., French J., Richter R., Franco-Buff A., Johnson A., Hillier S., Judson F. N. & Todd J. K. (1990) Antenatal microbiological maternal risk factors associated with prematurity. *Am J Obstet Gynecol* **163,** 1465-1473.

Minkoff H., Grunebaum A. N., Schwarz R. H. *et al.* (1984) Risk factors of prematurity and premature rupture of membranes. A prospective study of the vaginal flora in pregnancy. *Am J Obstet Gynecol* **150,** 965-972.

Polk B. F and other investigators of the John Hopkins Study of cervicitis and adverse pregnancy outcome (1989) Association of *Chlamydia trachomatis* and *Mycoplasma hominis* with intrauterine growth retardation and preterm delivery. *Am J Epidemiol* **129 (6),** 1247-1257.

Quinn P A. (1988) Mycoplasma infection of the fetus and newborn. In *Transplacental Effects on Fetal Health,* Alan R. Liss Inc., pp 107-151

Regan J. A., Chao S. & James L. S. (1981) Premature rupture of membranes, preterm delivery and group B streptococcal colonization of mothers. *Am J Obstet Gynecol* **141,** 184-186

Reimer L. G. & Reller L. B. (1984) *Bacterial vaginosis* and postpartum infection. *Obstet Gynecol* **64,** 170-175.

Romero R., Brody T., Oyarzun E., Mazor M., King Wu Y., Hobbins J. C. & Durum S. K. (1989) Infection and Labour III. Interleukin-I: A signal for the onset of parturition. *Am J Obstet Gynecol* **160,** 1117-1123.

Spiegel C. A., Amsel R., Eschenbach D., Schoenknecht F. & Holmes K. K. (1980) Anaerobic bacteria in non-specific vaginitis. *New Engl J Med* **303,** 601-607.

Taylor-Robinson D. & McCormack W. M. (1980) The genital mycoplasmas. Part I. *New Engl J Med* **302,** 1063-1067.

Received 30 May 1991
Accepted 24 September 1991

British Journal of Obstetrics and Gynaecology
March 1992, Vol. 99, pp 197–202

OBSTETRICS

Can out-of-hours work by junior doctors in obstetrics be reduced?

MARTIN McKEE
Senior Lecturer in Public Health Medicine
PATRICIA PRIEST
Research Officer
MARIA GINZLER
Research Officer
NICK BLACK
Senior Lecturer in Public Health Medicine

Health Services Research Unit
London School of Hygiene and
Tropical Medicine
Keppel Street
London WC1E 7HT, UK

ABSTRACT

Objective Against a background of concerns about the hours of work of junior doctors, this study examines how the night-time work of junior staff in obstetrics may be reduced by giving greater responsibility to midwives.

Design In the first phase of the study, the tasks undertaken at night in four hospitals were identified. In the second phase a nominal group technique was used to seek the extent of agreement among professionals about the appropriateness of postponing surgery to the following day in certain circumstances.

Results There were considerable variations between hospitals in the rate of obstetric intervention and the division of tasks between doctors and midwives. The panel concluded that many tasks currently performed by senior house officers could be undertaken by midwives.

Conclusion This study suggests that there scope for reducing the workload of junior obstetricians at night through the adoption of an extended role by midwives.

In 1989 a report published by the British Postgraduate Medical Federation (BPMF) (Dowie 1989) drew attention to the intensity of work of junior doctors in obstetrics and gynaecology. They are one of the busiest groups of doctors in a hospital at night, exceeded only by paediatricians. The BPMF report, and a subsequent agreement by the Ministerial Group on Junior Doctors' Hours (Department of Health, Welsh Office, DHSS—Northern Ireland and Scottish Home and Health Department 1990) have called for research as to how the volume of work can be reduced and, in particular, whether some tasks might be delegated to other professionals. The division of tasks between doctors and nurses is known to vary among hospitals (Green *et al.* 1986), although there has been little work to determine whether a consensus on this topic can be reached. We report the results of such a study.

Methods

The study was performed in two phases. In the first phase the tasks undertaken by junior doctors in four NHS hospitals were identified. They included one teaching hospital and district general hospitals in inner and outer London and in a rural district about 50 miles from London.

Two main sources of data were used: routine records and diaries. Data from labour ward registers were extracted in respect of all births from 1700 hours to 0900 hours during 4 months. Diaries completed by junior medical staff, designed following a pilot study in one of the hospitals, were used to record all activities undertaken between 1700 hours and 0900 hours over a 7-day period. Diaries were completed by 11 senior house officers (SHOs), four registrars and a senior registrar. The information recorded included whether the activity was self-initiated or as a result of a request from other staff, the time of commencement, details of the request, and the activity undertaken. The doctors described the activities in their own words. These data were supplemented by interviews with five SHOs, two registrars, a senior registrar and groups of midwives in three of the hospitals, and by comments enclosed with the diaries. A report was compiled using information collected during this phase, supplemented with a review of relevant literature.

In the second phase a panel of professionals was convened consisting of five consultant obstetricians, two registrars in obstetrics, and two midwives. A nominal group technique described by Glaser (1980) was employed. Between 6 and 8 weeks before the date of the panel, each participant was sent a summary of the findings of the descriptive phase and a review of relevant literature accompanied by a first round questionnaire which sought the views of panellists about the division of tasks between doctors and midwives. The responses to this first round questionnaire were used to generate second round questionnaires for use in the panel meeting. The meeting occupied a half-day. Participants were given lunch and reimbursed for travelling expenses, but there was no other payment.

After an introductory explanation, participants discussed each item on the questionnaire. At the end of the discussion on each question they were asked to rate the appropriateness of medical involvement on a 9-point scale in which 1 indicated

Correspondence. Dr Martin McKee

Table 1. Activities recorded in diaries

	No. of episodes (% of grand total) recorded by							
Activity	SHO (n = 11)		Registrar (n = 4)		SR (n = 1)		All (n = 16)	
(1) Clinical tasks								
Review patient	83	(26)	19	(23)	4	(19)	106	(25)
Attend delivery	9	(3)	8	(10)			17	(4)
Prescribe drugs	14	(4)					14	(3)
Ward round	7	(2)	2	(2)	2	(10)	11	(2)
Review fetal heart trace	7	(2)	2	(2)			9	(2)
Prescribe i.v. fluids	7	(2)					7	(2)
Do ultrasound scan	1	(0)	2	(2)	1	(5)	4	(1)
Order X-rays	2	(1)					2	(0)
Obtain consent for treatment	2	(1)					2	(0)
Total	132	(41)	33	(40)	7	(33)	172	(41)
(2) Technical tasks								
Induce labour	11	(3)	2	(2)			13	(3)
Re/site i.v. infusion	12	(4)					12	(3)
Suture tears/episiotomies	11	(3)	1	(1)			12	(3)
Give i.v. drugs	8	(2)					8	(2)
Blood sample — venous	7	(2)					7	(2)
Add drugs to infusion	4	(1)					4	(1)
Do ECG	2	(1)					2	(0)
Commence epidural anaesthesia	1	(0)					1	(0)
Fetal blood sampling	1	(0)					1	(0)
Insert urinary catheter	1	(0)					1	(0)
Total	58	(18)	3	(4)			61	(14)
(3) Administrative/clerical tasks								
Liaise with other agency	14	(4)	4	(5)			18	(4)
Organise blood transfusion	5	(2)					5	(1)
Pursue results/arrange transport	4	(1)					4	(1)
Clinical meeting/audit					1	(5)	1	(0)
Collect drugs/equipment	1	(0)					1	(0)
Complete accident form	1	(0)					1	(0)
File results	1	(0)					1	(0)
Organize beds			1	(1)			1	(0)
Total	26	(8)	5	(6)	1	(5)	32	(6)
(4) Operating theatre tasks								
Operate/assist in theatre	11	(3)	11	(13)	7	(33)	29	(7)
Organize theatre	1	(0)					1	(0)
Total	14	(4)	11	(13)	7	(33)	30	(7)
(5) Admission related tasks								
Clerk patient	67	(21)	3	(4)			70	(16)
See patient in A&E	3	(1)	2	(2)	1	(5)	6	(1)
Advise doctors in A&E	2	(1)					2	(0)
Discharge patient	2	(1)					2	(0)
Total	74	(23)	5	(6)	1	(5)	80	(19)
(6) Advice								
Seek/give advice to/from other doctor	13	(4)	26	(31)	3	(14)	42	(10)
Advise nurses by phone	4	(1)					4	(1)
Advise GP by phone	1	(26)			2	(10)	3	(1)
See referral from other firm	1	(0)					1	(0)
Total	19	(6)	26	(31)	5	(24)	50	(12)
Grand total	332	(100)	94	(100)	28	(100)	425	(100)

SHO — senior house officer; SR — senior registrar.

that a doctor should always perform the task and 9 indicated that a doctor need never perform it. There was no pressure to produce agreement. At the conclusion of each panel the scores were analysed for the extent to which a consensus view existed. A record of the discussion was transcribed.

Agreement was said to exist if, after discarding one extreme

Table 2. Details of deliveries occurring between 1700 and 0900 hours during 4 months

	Hospital							
	A		B		C		D	
Births	682		686		556		665	
Caesarean sections (% of all births)	58	(8·5)	96	(14)	37	(6·7)	40	(6)
Forceps/ventouse (% of all births)	75	(11)	41	(6)	20	(3·6)	23	(3·5)
Normal (% of all births)	541	(79·3)	541	(78·9)	484	(87·1)	589	(88·6)
Twins (vaginal)	4		3		6		4	
Breech (vaginal)	4		5		9		9	
Tear/episiotomy (% of normal deliveries)	301	(55 6)	288	(53 2)	319	(65·9)	Not recorded	
Grade of staff repairing tears/episiotomies after normal deliveries (percentages of total)								
SHO	179	(59)	135	(47)	93	(29)	Not recorded	
Registrar	91	(30)	16	(6)	32	(10)		
Senior registrar	15	(5)						
Consultant	2		2	(1)	3	(1)		
Med student	1		6	(3)	2	(1)		
Midwife	13	(5)	124	(44)	189	(59)		
Total	301	(100)	283	(100)	319	(100)		
Grade of staff carrying out normal deliveries (percentages of total)								
SHO	15	(3)	8	(1)	1			
Registrar	27	(5)	2		9	(2)	2	
Senior registrar	3		3					
Consultant	1		1		2			
Med student	2		16	(3)	10	(2)		
Midwife	493	(91)	511	(94)	462	(95)	587	(99)

Source: Labour ward registers.

high and one extreme low rating, all seven ratings lay within a single 3-point range. Disagreement was defined as at least one of the remaining seven ratings as a 1–3 and at least one as a 7–9. Other combinations were referred to as partial agreement. The rationale for this scoring system has been described by Scott & Black (1991).

Results

Quantitative description of tasks

A list of tasks recorded by junior doctors in the four districts is shown in Table 1. Overall, 53% of activities involved examining or treating patients previously admitted and advising other staff. Tasks related to admissions accounted for 19% of tasks, and operating accounted for a further 7%. Another 14% were technical tasks, such as starting intravenous infusions and repairing perineal trauma. Finally, 6% of tasks were essentially clerical or administrative. Not surprisingly, these proportions varied by job status — SHOs did more technical tasks, senior registrars more operating and advising.

It has not been possible to separate completely those tasks performed when on call for obstetrics from those which relate to gynaecology because of the degree of overlap. Nonetheless, certain tasks are clearly related, to a greater or lesser degree, to one or the other.

Inter-hospital comparisons

As only a small number of doctors completed diaries, detailed quantitative comparisons of workload between hospitals is not possible. However, labour ward registers provided some evidence of variation (Table 2). Although the total numbers of births at night in the four hospitals were similar, the involvement of doctors appears to vary considerably. This partly reflects differences in intervention rates. For example, the night-time caesarean section rate in hospital B is over twice that in hospital D. There are also, however, differences in policy. Doctors are much more likely to perform a normal delivery in hospital A than elsewhere, although the total numbers are small. Also in hospital A, doctors repair 95% of tears and episiotomies, whereas the corresponding figures in hospitals B and C are 56% and 41%. Further evidence of differences in policy on the division between doctors and midwives was obtained from interviews (Tables 3 and 4). These reflected important cultural differences. For example, after the data collection had been completed in hospital A, certain changes were instituted, giving midwives a much greater role. Until then the prevailing culture was dominated by a medical approach. This contrasted with hospital D where midwives had a high degree of autonomy.

Attitudes of doctors and nurses

Midwives in hospital D expressed considerable job satisfaction, whereas in other hospitals they expressed frustration at what they perceived as petty barriers to their autonomy such as: "to suture episiotomies you have to see the same registrar, suture three times and he must supervise you three times. It's very difficult to get it all done with the same registrar" and: "I gave i.v.s for 10 years and was told that my qualification was too old so I must stop doing them and retrain".

Table 3. Grade of staff usually performing tasks in obstetrics

	Hospital			
Task	A	B	C	D
Suture episiotomies & uncomplicated perineal tears	SHO	MW	SHO (most) MW (some)	MW
Apply scalp electrodes	MW (most) Reg (some)	MW	SHO (most) MW (some)	MW
Intubate infants	Paed SHO	Paed SHO	Paed SHO MW (some)	Paed SHO
Vacuum extraction	Reg	SHO	Reg	Reg
Perform low forceps	Reg	Reg/SHO	Reg	Reg
Set up i.v. infusions	SHO	SHO	SHO	SHO
Give epidural top-ups	Anaesthetist SHO	MW & anaes SHO	N/A	N/A
Deliver breech	Reg	Reg	Reg	Reg
Deliver twins (both vertex)	MW Reg present	MW Reg present	Reg	MW
Counsel parents after stillbirth	Reg/Cons	Cons	Cons	Reg/MW
Clerk normal admissions	MW + SHO*	MW + SHO	MW + SHO	MW + SHO

MW = midwife; SHO = senior house officer, Reg = registrar; Paed = paediatric, Cons = consultant; N/A = not applicable.
*During November 1989 SHOs ceased clerking routine admissions who were expected to have normal deliveries.
Source: Interviews with registrars and SHOs.

Frequently both midwives and SHOs were in favour of change but senior staff had either failed to promote, or had actively obstructed change. For example, midwives and SHOs felt that it was unnecessary for SHOs to clerk those women who were expected to have normal deliveries. "The SHO usually just copies out what the midwife has found" (midwife) — and: "there's a directive that the SHO has to see every woman in labour. The midwives have fought it — it undermines them. I look at the midwife's cardex and I copy it down. I feel the woman's belly and I introduce myself" (SHO).

The administration of intravenous drugs is a further area of contention. Some SHOs considered that midwives were being unreasonable when they refused to administer i.v. drugs because they had obtained a certificate at another hospital that was not valid elsewhere. Whereas the midwives felt that this was an obstacle placed in their way by their own managers, and that they were being criticised unfairly by the SHOs.

Conclusions of panel

The panel were asked to consider tasks related to childbirth that did not clearly require a doctor. In addition, it was felt important to consider who should make the decision as well as who carried it out. The conclusions of the panel on the topics considered are shown in Tables 5 and 6. Many of the topics provoked considerable discussion, leading to qualification of some of the conclusions. The key points arising were as follows.

While repair of an episiotomy or uncomplicated tear usually need not be done by a doctor, where the woman had sustained previous perineal damage, the repair should be by a registrar.

Panellists remarked on the variation in the extent to which midwives are permitted to intubate infants. It was noted that, unlike junior doctors, midwives receive specific training in this. Parental expectation of medical involvement was thought unlikely to be a problem providing the individual concerned was properly trained.

Although the panel was asked to decide if a doctor should perform breech or twin delivery, panellists interpreted this as a question of whether a doctor should be present. There was general agreement that the doctor should be a registrar as

Table 4. Grade of staff usually making clinical decisions normal deliveries

	Hospital			
Decision	A	B	C	D
When to do VE in labour	Reg/MW	MW	MW/SHO/Reg	MW
When to rupture membranes	Reg/MW	MW	MW if>4 cm	MW if>3 cm
Whether to give i.m. analgesia	Pt/MW	Pt/MW	Pt/MW	Pt/MW
To use oxytocin	Pt/Reg/MW	SHO	SHO/Reg	Reg/SHO
To do episiotomy	Pt/MW	MW	MW	MW
To discharge (no complics)	MW	SHO	MW	MW
To discharge (complics)	Reg	SHO	SHO	SHO
To call registrar	MW/SHO	MW/SHO	MW/SHO	MW/SHO

Pt = patient; MW = midwife; SHO = senior house officer, Reg = registrar, VE = vaginal examination.
Source: Interviews with registrars and SHOs.

Table 5. Appropriateness of tasks being performed by a midwife

Task	Level of agreement	Median	Appropriateness of being done by a midwife
Suture episiotomy	A	7	Appropriate
Suture an uncomplicated perineal tear	A	7	Appropriate
Apply scalp electrodes	A	8	Appropriate
Intubate infants	PA	6	Equivocal
Set up i.v. infusions	A	8	Appropriate
Administer epidural top-ups	A	8	Appropriate
Perform a breech delivery	A	1	Inappropriate
Deliver twins (both vertex)	PA	1	Equivocal
Clerk patients admitted in labour	PA	7	Equivocal

immediate operative delivery may be required. It was noted that as more breech deliveries are by caesarean section there is a danger of staff failing to gain adequate experience of vaginal breech delivery.

Clerking a woman admitted in labour generated considerable debate. Two issues emerged: the line of responsibility for the patient and the ability of midwives to recognise medical abnormalities. In the first instance, some consultants felt that if they are ultimately responsible for the woman, she should be seen by their SHO, whom they see as someone over whom they have clearly defined control. Without this control they were concerned about potential medico-legal complications. However, midwives pointed out that they are responsible in law for their own decisions. In the second instance some panellists argued that midwives would not have the skills required to identify pre-existing medical conditions. This was countered by the contention that many of these would be identified during antenatal care, and the reminder that all midwives have several years experience as registered general nurses. These views could not be reconciled, although, as several panellists indicated, a policy of all women being seen by a junior doctor on admission has substantial implications for out-of-hours workload.

Consideration of decision-making in labour wards should be seen in the context of many units having agreed guidelines. Thus the questions related to whether or not midwives should be authorized to make decisions that did not comply with existing guidelines. There was debate about the role of guidelines in obstetrics, and especially whether they remove autonomy from midwives and reduce the involvement of the women in their deliveries. Although the questions considered whether midwives rather than doctors should make certain decisions, several emphasized that the woman should be involved. Thus, while a midwife is felt to be competent to make most of the decisions considered, the use of oxytocin should be made by a midwife and doctor together, as it converts a normal labour to one that is abnormal. Several panellists argued that a midwife will have more experience than an SHO, and therefore the doctor involved should be a registrar.

The concern that an expanded midwifery role would reduce the training experience of junior medical staff was raised repeatedly. For example, if repair of perineal trauma is to become a midwifery responsibility it may be very difficult for SHOs to gain the appropriate skills. Some, however, suggested that it could be learnt under supervision during the day.

Conclusions

Within the four hospitals studied there was considerable variation in the workload of doctors and the division of tasks between doctors and midwives. This small sample understates the extent of variation within the United Kingdom. For example, a study of six units (Green *et al.* 1986) found that several tasks, such as epidural top-ups and intravenous infusions,

Table 6. Appropriateness of decisions being made by a midwife

Decision	Level of agreement	Median	Appropriateness of being decided by a midwife
When to do a VE in labour	A	8	Appropriate
When to rupture membranes	A	7	Appropriate
Whether to give i m. analgesia	A	8	Appropriate
Whether to use syntocinon	A	1	Inappropriate
Whether to do an episiotomy	A	8	Appropriate
When to transfer to community (uncomplicated birth)	A	8	Appropriate
When to transfer to community (after complications)	PA	2	Equivocal
When to call a registrar	A	9	Appropriate
To discharge a patient not in labour	PA	8	Equivocal

Interpretation: 1 — must be done by a doctor; 9 — need never be done by a doctor.
A — agreement; PA — partial agreement; D — disagreement
VE — vaginal examination.

were performed by midwives in some hospitals, unlike any of the hospitals in the present study. The availability of skills seems to have relatively little effect on practice. For example, only 55% of consultant units in the United Kingdom have midwives who regularly suture the perineum (Garcia *et al.* 1985), although this is now part of the basic midwifery syllabus (Sleep 1987).

Consensus development offers an approach to the development of local guidelines whereby widespread involvement in decision-making can be achieved, and in which agreement and disagreement can be identified. It is important to recognize, however, that the existence of a consensus does not in itself mean the view is correct. There is a danger that the nominal group process will arrive at collective ignorance rather than wisdom. As such it is not a replacement for rigorous scientific reviews of published literature, but rather a means of determining locally how much support a given clinical guideline is likely to receive. It also serves to identify areas of disagreement that the participants might be encouraged to explore through further research.

With these provisos, the panel concluded that many of the tasks and decisions associated with normal labour do not require the presence of a doctor, and most of those at present undertaken by SHOs out of hours could be done by midwives. When a doctor is required, he or she should generally be a registrar. It is not possible to relate the panel's conclusions directly to the data recorded in the diaries, but our best estimate is that it may be possible to reduce the number of tasks performed by up to 20%.

The panel's conclusions raise important questions about the role of the SHO in obstetrics. There are two principal types of doctor involved. The majority are on general practice vocational training programmes and do not intend to pursue a career in the speciality (Hill *et al.* 1983). In many hospitals very few SHOs will have more than 6 months experience while the small number who plan to stay in the specialty may have been working in obstetrics for 3 or more years. The limited ability and experience of the SHO has led some consultants to advocate that it is essential to have resident registrars (Hill *et al.* 1983), although others have argued that a consultant SHO team is acceptable (Pentecost, 1983).

Only a small minority of general practice vocational trainees will be involved in the management of labour in their subsequent careers. It is therefore difficult to see the relevance for most SHOs of learning how to do practical procedures on a labour ward. Conversely it could be argued that those few trainees who are planning to take responsibility for women in labour as general practitioners will require more than 6 months training.

A key issue underlay the discussion but remained unanswered: who should be responsible for a normal delivery. At the risk of over-simplification, the arguments advanced by those advocating medical leadership are based on the premise that a delivery can only be known to be normal after it is over, whereas those advocating a central role for midwives argue that deliveries are normal until discovered to be otherwise (Walker 1986; Flint 1979). Proponents of both views accept the need for medical involvement in the presence of complications. A greater role for midwives is supported by the Royal College of Midwives (RCM 1987) and the Association of Radical Midwives (ARM 1986). Both favour the midwife taking over from the general practitioner as the first point of contact for pregnant women, and argue that midwives should manage normal labours, with direct access to laboratory investigations and referral to other professionals as necessary. These views are supported by studies which demonstrate that midwives can achieve perinatal outcomes which are similar to, or better than, those achieved by doctors (Slome *et al.* 1976).

Many proponents and opponents of this approach have strongly held views, and it is unlikely that they will be reconciled easily. Nevertheless, it may be possible to set aside the more contentious issue of ultimate clinical responsibility for patients and produce clear educational guidelines and training requirements for each of the different types of obstetric SHO. This would help to reduce the hours worked by junior doctors and possibly increase the value of their training.

Acknowledgments

This work received financial support from the Department of Health. We are grateful to the participants in the panel and to the medical and nursing staff of the hospitals concerned. The views expressed are those of the authors alone.

References

Association of Radical Midwives (1986) *The Vision: Proposals for the Future of the Maternity Services* Association of Radical Midwives, Ormskirk, Lancs.

Department of Health, Welsh Office, DHSS—Northern Ireland and Scottish Home and Health Department (1990) *Heads of Agreement—Ministerial Group on Junior Doctors' Hours.* DoH, London.

Dowie R. (1989). *Patterns of Medical Staffing.* Interim Report. BPMF, London.

Flint C. (1979) A continuing labour of love. *Nursing Mirror,* **15,** Nov 1979, 16-18.

Garcia J., Garforth S. & Ayers S. (1985) *Midwives Confined? Labour Ward Policies and Routines* Paper presented to conference on Research and the Midwife, Manchester.

Glaser E M. (1980) Using behavioural science strategies for defining the state-of-the-art. *J Appl Behav Sci* **16,** 79-92.

Green J., Kitzinger J & Coupland V. (1986) *The Division of Labour* Child Care and Development Group, University of Cambridge, Cambridge.

Hill J. G., Taylor R. W. & Basu H. K. (1983) Manpower imbalance in obstetrics and gynaecology. *Br Med J* **286,** 1159-1162.

Pentecost A.(1983) Is there another consultant lifestyle? *Br Med J* **287,** 305-306.

Royal College of Midwives (1987) *The Role and Education of the Future Midwife in the United Kingdom* Royal College of Midwives, London.

Sleep J. (1987). Perineal management — a midwifery skill under threat. *Midwife Health Visitor Community Nurse* **23,** 455-458.

Scott E. A. & Black N. A. (1991) When does consensus exist in expert panels? *J Publ Health Med* **13,** 35-39

Slome C., Wetherbee H., Daly M., Christensen K., Meglen H. & Thiede H. (1976) Effectiveness of certified nurse-midwives: a prospective evaluation study. *Am J Obstet Gynecol* **124,** 177-182.

Walker J. F. (1976) Midwife or obstetric nurse? Some perceptions of midwives and obstetricians on the role of the midwife. *J Adv Nurs* **1,** 129–138.

Received 26 April 1991
Accepted 26 August 1991

British Journal of Obstetrics and Gynaecology
March 1992, Vol. 99, pp. 203–206

OBSTETRICS

Determinants of caesarean section rates in Italy

FABIO PARAZZINI
Istituto di Ricerche Farmacologiche
Mario Negri, Milan, Italy

NICOLETTA PIROTTA
Consorzio Interuniversitario Lombardo
per l'Elaborazione Automatica
Milan, Italy

CARLO LA VECCHIA
Istituto di Ricerche Farmacologiche
Mario Negri, Milan, Italy

LUIGI FEDELE
Prima Clinica Ostetrico-Ginecologica
Università di Milano
Milan, Italy

ABSTRACT

Objective To analyse the determinants of caesarean section rates in Italy.
Design Analysis of information using a standard form on all the deliveries after the 28th week of gestation routinely collected by the Italian Central Institute of Statistics
Setting National data of all Italian deliveries in the periods 1980–1983.
Subjects A total of more than 2 400 000 deliveries occurred in Italy in the period and are considered in this analysis.
Results The frequency of caesarean section rose from 11·2/100 deliveries in 1980 to 14·5/100 in 1983. Caesarean section rates were lower in the Southern (less rich) areas, and rose steadily with maternal age, being about three times higher in women aged ⩾40 years than in teenagers. Maternal education was directly associated with caesarean section rates: compared with women with only primary school education, those with a college education reported an about 40% higher rate of caesarean section, but this difference dropped markedly after allowance for maternal age and birthweight. The section rate was 13·3/100 deliveries in public hospitals and 11·8/100 in private ones, but this reflected the different utilization of public and private services in various geographical areas. Birthweight and gestational age at delivery were important determinants of caesarean section rates; lowest values were observed for very-low-birthweight and very preterm deliveries and babies weighing 3000–3999 g and term deliveries. Caesarean section rates were about 20% higher in nulliparous than in parous women and the rates increased with number of stillbirths or miscarriages; further, the rate ratio was about double in multiple than in single births
Conclusion Caesarean section rates in Italy in the early 1980s were still lower than in North America, but their determinants share several similarities with those reported in other areas.

There have been substantial increases in the frequency of caesarean section in developed countries (Taffel *et al.* 1987; Notzon *et al.* 1987). For example in the United States caesarean section rates were about 5% of deliveries in 1965, but rose to 24% in 1987 (Taffel *et al.* 1987).

Many factors have been put forward to explain this upward trend, including repeat caesarean section, the increasing early recognition of fetal distress by fetal monitoring techniques, changing childbearing patterns (i.e., increased frequency of older primiparous mothers) and the decreasing use of forceps (Taffel *et al.* 1987; Notzon *et al.* 1987; Shiono *et al.* 1987). For example, in the United States forceps deliveries declined from 37% in 1972 to 18% of all deliveries in 1980 (Placek *et al.* 1983).

Besides obstetric indications and fear of malpractice suits, socio-economic factors have been proposed as having a role in the frequency of caesarean section. Several reports, generally from the United States, have shown that higher social class (Gould *et al.* 1989), as well as private (or clinic) care (Haynes de Regt *et al.* 1986; Placek *et al.* 1988; Kizer & Ellis 1988; Williams & Chen 1983), are associated with more frequent caesarean sections. These associations were independent of age, parity, birthweight and obstetric fetal complications (Gould *et al.* 1989).

In Europe the frequency of caesarean section has been steadily rising, although in most European countries the rate is still 30–50% lower than in the United States or Canada. For example, in the early 1980s the rate ranged from 5 to 7% of deliveries in Belgium, Austria, Czechoslovakia and from 11 to 12% in France and Scandinavian countries (against 16–18% in the USA and Canada) (Notzon *et al.* 1987; Thiery *et al.* 1989).

Few data are available on the obstetric and socio-economic determinants of caesarean section in Southern European countries. Therefore, this article considers rates and determinants of caesarean section in Italy, using information routinely collected on more 2 400 000 deliveries in 1980–1983 (Parazzini *et al.* 1990).

Methods

In Italy, information on the deliveries after the 28th week of gestation are routinely collected by law using a standard form by the Italian Central Institute of Statistics. Data collected include: maternal and fetal characteristics, and the modalities

Correspondence Dr Fabio Parazzini, Istituto di Ricerche Farmacologiche, "Mario Negri", Via Eritrea 62, 29157 Milano, Italy.

Table 1. Caesarean section rates according to calendar year, geographical area, place of birth and selected maternal characteristics, Italy, 1980–1983

	Number of caesarean sections*	Caesarean section rate/100 deliveries	
		Crude	Standardized†
Total	322 363	12·9	–
Calendar year			
1980	72 447	11·2	–
1981	79 641	12·7	–
1982	82 430	13·2	–
1983	87 845	14·5	–
Geographic area			
North	135 172	14·9	14·8
Centre	64 224	15·1	15·0
South	122 967	10·5	10·7
Maternal age (years)			
≤19	13 860	8·7	8·3
20–24	78 760	10·5	10·5
25–29	103 688	12·5	12·4
30–34	76 456	15·0	14·8
35–39	36 662	19·5	19·6
40–44	10 738	24·3	25·2
≥45	773	24·2	25·2
Maternal education			
College (≥14 years education)	19 042	17·0	14·1
High school (9–13 years education)	73 269	14·0	13·9
Intermediate school (6–8 years education)	121 439	12·4	12·9
Primary school (≤5 years education)	107 191	12·3	11·9
Place of birth			
Public hospital	282 526	13·3	13·3
Private hospital	38 394	11·8	11·5

*In some cases the sum does not add up to the total because of missing values.

†Directly standardized for maternal age, education and birthweight.

of delivery. Forms are completed by the midwives or the physician at the time of delivery.

We obtained copies of the original computer tapes including records of all deliveries in Italy in the period 1980–1983. More recent data are not available at the time of writing this report due to delay in preparing the computer tapes by the Central Institute of Statistics.

From these records we extracted information on caesarean or vaginal delivery, maternal age and education and obstetric history, place of birth, fetal sex, gestational week at birth, birthweight, presentation and multiple pregnancy.

The proportion of caesarean sections per 100 deliveries (caesarean section rate) was computed per calendar year and for the total quadriennium in strata of the various maternal and fetal characteristics. Caesarean section rates standardized for maternal age and education and birthweight were derived by the direct method (Armitage 1971) using the total population of deliveries as standard.

Results

Table 1 considers caesarean section rates according to calendar year, geographical area, selected maternal characteristics and place of birth. In the period considered, the frequency of caesarean section rose steadily from 11·2% deliveries in 1980 to 14·5% in 1983. There were marked geographical differences in caesarean section rates, which were about 40% lower in the Southern (less rich) areas than in the North or Centre of Italy. The rate of abdominal deliveries increased with maternal age, being, about three times higher in women aged ≥40 years than in teenagers. Compared with women with primary (i.e., ≤5 years of education) or intermediate schooling (6–8 years), those with a college education reported an about 40% higher rate of caesarean sections. This difference, however, was reduced after taking into account maternal age and birthweight, and it is possible that the some of residual difference is due to underadjustment for these variables.

The proportion of caesarean sections was 13·3% of deliveries in public hospitals and 11·8% in private ones; the difference did not change after allowance for covariates. However, analysis of the data according to the three broad Italian geographical areas (North, Centre and South) showed lower caesarean section rates in private hospitals in the South (11·5% of deliveries in public hospital and 8·1% in private clinics), but the frequency of birth by caesarean section was about 30% higher in private hospitals in the North and Centre of Italy (public and private hospital rates were respectively 14·7 and 18·5% of deliveries in the North and 14·6 and 19·6% in the Centre).

Obstetric determinants of caesarean section rates are considered in Tables 2 and 3. There were non linear relations between caesarean section rates and birthweight and ges-

Table 2. Caesarean section rates according to birthweight and gestational age Italy, 1980–1983

	Number of caesarean sections*	Caesarean section rate/100 deliveries	
		Crude	Standardized†
Birthweight (g)			
<1000	768	10·2	9·8
1000–1499	2 638	19·1	19·0
1500–1999	6 199	23·7	23·5
2000–2499	17 476	18·8	18·9
2500–2999	58 742	14·3	14·4
3000–3499	123 226	11·9	12·1
3500–3999	84 006	11·8	11·8
4000–4499	24 539	13·6	13·5
≥4500	4 680	16·3	16·4
Gestational age (weeks)			
25–27	420	8·4	5·7
28–31	3 004	17·0	14·1
32–36	24 363	11·7	9·1
37–41	281 322	12·9	13·0
≥42	13 135	16·0	16·3

*In some cases the sum does not add up to the total because of missing values

†Directly standardized for maternal age, education and birthweight (for week of gestation at delivery).

tational age at birth. The values were lowest for very-low-birthweight (<1000 g) and deliveries between 25 and 27 weeks gestation; they increased in subsequent strata of weight or weeks (up to 3000 g or 31 weeks), but decreased again in term births and in babies weighing 3000–3999 g at birth (about 12% deliveries in these strata). Finally, they rose to about 16% deliveries in post-term or in high-birthweight (≥4500 g) babies (Table 2).

Only 3% of all deliveries were breech presentation, but 55% of those were delivered by caesarean section and percentages were similar for shoulder presentation (0·1% of all deliveries) and slightly lower (about 40–45%) for other abnormal presentations (Table 3). Nulliparae were at a higher risk of caesarean section than parous women and the risk increased after allowance for maternal age, education and birthweight. The caesarean section rate increased with numbers of stillbirths and miscarriages and was about double in multiple than in single births (Table 3).

Discussion

The frequency of caesarean section increased steadily in Italy in the early 1980s, although the 14% rate for 1983 was still appreciably lower than American values in the same calendar period (Taffel *et al.* 1987). The present analysis covered only the period 1980–1983, but data available for selected areas suggest that the same upward trend was present in the middle 1980s, too (Bertolini *et al.* 1987).

The present study has both strengths and limitations of the analyses of vital statistics. Its major strength and interest lies, of course, in the nation-wide coverage of all deliveries and the large data set (more than 2 400 000 deliveries). The quality and completeness of data were generally satisfactory. For example there were no missing values for mode of delivery (vaginal or abdominal) or birthweight and only 0·5% of the records failed to report maternal age (Parazzini *et al.* 1990). Further, the present analysis considered only 'hard' maternal variables, such as age, education and parity, which are unlikely to be substantially affected by recall, classification or collecting bias.

The major drawback of the analysis is the lack of data on obstetric complications (i.e., dystocia, fetal distress) and previous caesarean section in parous women. However, standardization for birthweight did not markedly influence the differences in the frequency of caesarean sections, suggesting that a large proportion of them is unlikely to be due to a different baseline distribution of obstetric disorders.

The Italian caesarean section rate of about 14% deliveries compares well with available data for France in the same calendar period (Notzon *et al.* 1987), but is at least 40–50% higher than those of other European countries such as Belgium or Austria (Notzon *et al.* 1987). Large differences in caesarean section rates also emerged among the three main Italian geographical areas: the Southern (less rich) areas of the country reported an about 40% lower rate than the North or Centre.

Maternal age was a strong determinant of caesarean section rates in Italy; the rate in women aged ≥40 years was about three times the rate reported in teenagers. Similar ratios between age groups were observed in other countries, independently from their baseline caesarean section rates (Gould *et al.* 1989; Thiery *et al.* 1989; Yudkin & Redman 1986).

Over 50% of babies presenting by the breech were born by caesarean section. This is about one third lower than the per-

Table 3. Caesarean section rates according to selected obstetrical variables Italy, 1980–1983

	Number of caesarean sections*	Caesarean section rate/100 deliveries	
		Crude	Standardized†
Type of birth			
Single	312 307	12·7	12·8
Multiple	10 056	21·5	23·8
Presentation at birth			
Vertex	275 775	11·5	11·6
Breech	34 377	55·3	62·1
Shoulder	2 975	56·7	53·3
Face	1 327	36·7	37·0
Brow	1 324	46·9	46·7
Bregma	764	20·9	21·1
Other	4 823	22·4	22·3
Previous pregnancies			
0	165 687	14·2	17·0
1	102 957	12·5	12·3
2	34 357	10·9	10·0
≥3	19 362	10·0	9·1
Previous stillbirths/miscarriages			
1	7 213	21·7	22·8
2	1 911	29·5	27·6
≥3	754	35·8	29·3

*In some cases the sum does not add up to the total because of missing values.

†Directly standardized for maternal age, education and birthweight.

centage in the United States in the late 1970s (Placek & Taffel 1983), but the ratio of breech-to-other presentations within caesarean sections (about 5) is consistent with that reported in the USA (Taffel *et al.* 1987; Placek & Taffel 1983).

In this analysis, socio-economic indicators appeared to be important determinants of caesarean section rates. Women of higher social class reported about 30–40% higher rates. Similar evidence—perhaps more marked—emerged from several studies conducted in the United States (Gould *et al.* 1989; Haynes de Regt *et al.* 1986; Placek *et al.* 1988; Kizer & Ellis, 1988; Williams & Chen 1983). For example a survey conducted in 1982–1983 in Los Angeles County showed that women who lived in census tracts with a median family income of more than 30 000 dollars had a primary caesarean-section rate of 23%, as compared with 13% among women residing in areas with a median family income under 11 000 dollars (Gould *et al.* 1989). Only about 10% of this difference could be accounted for by difference in parity and 30% in birthweight distribution. In our analysis, too, caesarean section rates were about 20% higher among more educated women after standardization for age and birthweight.

In Italy the frequency of caesarean section was lower for deliveries in private hospitals than in public ones. At first sight, this finding contrasts with data from the United States (Haynes de Regt *et al.* 1986; Placek *et al.* 1988; Kizer & Ellis, 1988; Williams & Chen 1983). However, a more detailed analysis of the data according to the three broad Italian geographical areas (Parazzini *et al.* 1990) showed that this apparent abnormality was largely attributable to a lower frequency of caesarean section in private hospitals in Southern Italy. This area includes a large number of private, low technology obstetric units that have special agreements with the Italian National Health Service, whereby patients are not charged for medical expenses (sometimes only for accommodation). In the North and Centre of the country with a more 'traditional' pattern of public and private medicine, caesarean sections were about 25% more frequent in private clinics.

In conclusion, caesarean section rates in Italy in the early 1980s were still lower than in North America, but their determinants share several similarities with those reported in other high or low rate areas. This observation suggests that the explanations for most of the intra-country or international differences in caesarean section rates should be sought in the 'physician factor' (Goyert *et al.* 1989) or in the organization of obstetric care, more than in different distributions of baseline obstetric and maternal determinants.

Acknowledgments

This work was conducted within the framework of the CNR (Italian National Research Council) targeted project Prevention and Control Disease Factors, subproject Disease Factors in Maternal and Infant Diseases. Ms Judy Baggott, Francesca Perego, Ivana Garimoldi and the G.A. Pfeiffer Memorial Library Staff provided helpful editorial assistance.

References

Armitage P. (1971) *Statistical Methods in Medical Research*, Blackwell, Oxford.

Bertolini R., Di Lallo D., Rapiti E. & Perucci C. A. (1987) Cesarean section rates in Italy. *Am J Public Health* **77**, 1554.

Gould J. B., Davey B. & Stafford R. S. (1989) Socioeconomic differences in rates of cesarean section. *N Engl J Med* **321**, 233-239.

Goyert G L., Bottoms S. F., Treadwell M. C. & Nehra P. C. (1989) The physician factor in cesarean birth rates. *N Eng J Med* **320**, 706-709.

Haynes de Regt R., Minkoff H. L., Feldman J. & Schwartz R. H. (1986) Relation of private or clinic care to the cesarean birth rate. *N Engl J Med* **315**, 619-624.

Kizer K. W. & Ellis A. (1988) C-sections rate related to payment source (letter). *Am J Public Health* **78**, 96-97.

Notzon F. C., Placek P. J. & Taffel S. M. (1987) Comparisons of national cesarean-section rates. *N Engl J Med* **316**, 386-389.

Parazzini F., Pirotta N., La Vecchia C. & Fedele L. (1990) I determinanti della mortalità perinatale ed infantile nelle regioni Italiane 1980–1983. Determinants of perinatal and infant mortality in the Italian regions 1980–1983. *Ann Ostet Ginecol Med Perinat* **111**, 9-146.

Placek P. J. & Taffel S. M. (1983) The frequency of complications in cesarean and noncesarean deliveries, 1970 and 1978. *Public Health Rep* **98**, 396-400

Placek P. J., Taffel S. M. & Keppel K. G. (1983) Maternal and infant characteristics associated with cesarean section delivery. Health, United States, 1983. DHHS Pub. No. (PHS) 84–1232. National Center for Health Statistics, Hyattsville, MD.

Placek P. J., Taffel S. M. & Moien M (1988) 1986 C-Section rise; VBACs inch upward. *Am J Public Health* **78**, 562-563.

Shiono P. H., McNellis D. & Rhoads G. G. (1987) Reasons for the rising cesarean delivery rates: 1978–1984. *Obstet Gynecol* **69**, 696-700.

Taffel S. M., Placek P. J. & Liss T. (1987) Trends in the United States cesarean section rate and reasons for the 1980–85 rise. *Am J Public Health* **77**, 955-959.

Thiery M., Deron R. & Buekens P. (1989) Frequency of cesarean deliveries in Belgium. *Biol Neonate* **55**, 90-96.

Williams R. L. & Chen P. M. (1983) Controlling the rise in cesarean section rates by the dissemination of information from vital records. *Am J Public Health* **73**, 863-867.

Yudkin P. L. & Redman C. W. G. (1986) Caesarean section dissected, 1978–1983. *Br J Obstet Gynaecol* **93**, 135-144.

Received 15 April 1991
Accepted 5 September 1991

British Journal of Obstetrics and Gynaecology
March 1992, Vol. 99, pp. 207–211

OBSTETRICS

Serum and intracellular magnesium during normal pregnancy and in patients with pre-eclampsia

JACQUES SEYDOUX
Department of Obstetrics and Gynecology
ERIC GIRARDIN
LUC PAUNIER
Department of Pediatrics and Genetics
FRANÇOIS BÉGUIN
Department of Obstetrics and Gynaecology
Hôpital Cantonal Universitaire de Genève
1211 Genève 4, Switzerland

ABSTRACT

Objective To determine the serum and lymphocyte magnesium concentrations during normal pregnancy and to compare the magnesium status in the third trimester of pregnancy between women with normal pregnancy and those with gestational hypertension (GH) or pre-eclampsia (PE).

Design A prospective cross-sectional study followed by a prospective comparative study.

Setting Department of Obstetrics and Gynecology, Department of Pediatrics and Genetics, Hôpital Cantonal Universitaire Genève, Switzerland.

Subjects Seventy-one healthy pregnant women, with normal pregnancies between 6 and 38 weeks gestation. The second part included 43 women in the third trimester of pregnancy, 11 had GH, 11 had PE and 21 formed the comparison group of healthy normotensive women.

Main outcome measures Total serum and intralymphocytic Mg concentrations and urinary Mg excretion.

Results There was a progressive reduction in total serum magnesium concentrations during normal pregnancy, thought to be partly due to haemodilution, because the decline in concentration of serum proteins paralleled that of Mg ($P<0.001$). In the three groups studied in the third trimester the serum Mg concentration was very similar in the GH and the comparison groups, but it was significantly higher in the PE group ($P<0.01$). The intralymphocytic Mg concentrations and the urinary Mg excretion were similar in all three groups. In five patients treated with MgSO4 there was a large increase in the serum Mg concentration and in the urinary Mg excretion. The intralyphocytic Mg concentration remained remarkably stable.

Conclusions Our data does not support the conclusion that Mg deficiency is the primary cause of pre-eclampsia.

Pre-eclampsia is a frequent complication of pregnancy and occurs in approximately 5–7% of pregnancies in Europe and the United States of America (Burrow & Ferris 1988; Pritchard *et al.* 1985).

The pathophysiological mechanism in pre-eclampsia is characterized by constriction of arterioles, leading to increased peripheral resistance and resulting in arterial hypertension. This vasospasm is associated with endothelial damage leading to platelet aggregation and fibrin deposits in the arterioles of various susceptible organs, which explains the multiplicity of clinical features and laboratory abnormalities. Despite intensive research during the past few decades, the cause of pre-eclampsia remains unknown. Recent medical investigations suggest that magnesium (Mg) deficiency could play an important role in the pathogenesis of pre-eclampsia, particularly in regulating the tonus of arterioles and veins (Seelig 1980; Altura *et al* 1983; 1984; Conradt *et al.* 1984b; Gunther 1985; Watson *et al.* 1986). Mg is primarily an intracellular cation and it is known that the extracellular Mg does not reflect the state of Mg balance, therefore Mg concentration was measured in the serum and in lymphocytes. The purpose of this study was to measure serum and intralymphocytic concentrations of Mg during normal pregnancy and to compare serum and intracellular Mg concentrations between women with hypertension in pregnancy and a comparison group of normal pregnancies.

Correspondence: Dr Jacques Seydoux, Division de Gynécologie et Obstétrique, Hôpital Regional, CH-2800, Delemont, Switzerland.

Subjects and methods

The first part of the study lasted 1 year and included 71 healthy pregnant women, aged 19–43 years with normal pregnancies between 6 and 38 weeks gestation. Women with essential hypertension, or who previously received Mg or diuretics and women with a previous history of renal disease were excluded. The second part of the study lasted also 12 months and involved 22 patients with hypertension according to the following criteria. Gestational hypertension (GH) was defined as a blood pressure of ≥140–90 mmHg, measured in the upper arm in the left lateral recumbent position in two or more occa-

Table 1. Characteristics of the women in the three study groups

Variable	Gestational hypertension (*n* = 11)	Pre-eclampsia (*n* = 11)	Normotensive (*n* = 21)
Age (years)	27·5 (6·6)	28·5 (4·6)	28·5 (4·6)
Gestational age (weeks)	37·2 (2·2)	35·2 (2·3)	36·2 (0)
Primiparous (%)	100	91	43
Blood pressure (mm Hg)			
Systolic	145 (6·6)	160 (9·9)	118 (9·1)
Diastolic	100 (6·6)	107 (6·6)	75 (4·6)
Proteinuria (g/24 h)	0,13 (0·07)	2·7 (2·3)	–
Haematocrit (%)	38·8 (2·3)	39·0 (3·6)	36 (2·3)

Data are mean (SD).

sions at 6 h intervals. Pre-eclampsia (PE) was defined as hypertension and proteinuria $\geqslant$300 mg/24 h, or >1 g/l in a random urine specimen. HELLP syndrome was diagnosed if there was evidence of haemolysis, elevated liver enzymes and a platelet count less than 100 × 10^9/l. All the hypertensive patients were admitted to the obstetric unit of the University Hospital of Geneva, Switzerland. They were studied between 32 and 40 weeks gestation. Of the 22 patients 11 had GH and the other 11 had PE. One patient in each group developed HELLP syndrome. In the PE group, two patients had gestational diabetes mellitus. A comparison group was selected in the last 3 months of our study comprising 21 healthy women with normal pregnancy who were attending the antenatal clinic for the first time in the third trimester, they had no history of essential hypertension, renal disease or ingestion of Mg or diuretics. All these women had normal pregnancies until delivery. Table I summarizes the characteristics of the three different groups. All the women in the study had a physical examination, ultrasound scan and antenatal fetal heart rate monitoring. All patients with hypertension (GH and PE) remained in hospital and had blood pressure, reflexes, proteinuria and fetal heart rate recorded twice daily. Some of them had an anmiocentesis to determine the lecithin: sphyngomyelin ratio. Induction of labour was performed if fetal lung maturity was confirmed in patients with increasing blood pressure and proteinuria. Where the patient's condition improved, blood pressure, reflexes, proteinuria and fetal heart rate monitoring were reviewed weekly until term. Patients with severe PE (diastolic blood pressure $\geqslant$110 mmHg and with abnormal neurological signs) were treated with magnesium sulphate as described by Pritchard *et al* (1985) except that we began with 2 g given intravenously and 10 g intramuscularly, but we did not systematically repeat the 5 g injection every 4 h. Intravenous hydralazine was also given, first as a bolus of 6·25 mg and than as a continuous infusion of 2·5 mg/h to a maximum of 15 mg/h. Labour was induced with oxytocin if the cervix was favourable; if the cervix was unfavourable delivery was by caesarean section.

On admission to hospital, venous blood samples were taken to measure intralymphocytic Mg concentration and plasma concentrations of Mg, sodium, potassium, calcium, creatinine, urea nitrogen, total protein, liver enzymes, haemoglobin and fibrinogen. The haematocrit, leucocyte count, platelet count, prothrombin time and partial thromboplastin time were also determined. Twenty-four hour urine specimens were collected for estimation of proteinuria, creatinine clearance and sodium, potassium and calcium excretion. Serum, lymphocytic and urinary Mg levels were measured during and after $MgSO_4$ treatment in the patients with severe PE. The same investigations were made in the 21 normal pregnant women at a comparable age of gestation.

Intracellular Mg concentrations were measured in lymphocytes as described by Elin & Johnson (1982) and modified by Girardin & Paunier (1985), within 2 h of sampling and expressed in relation to cell protein content. Plasma Mg concentrations were determined by atomic absorption spectrophotometry. Data analysis used the Mann Whitney *U*-test. *P* values of <0·05 were considered significant.

Results

Normal pregnancy

The pregnancies of all 71 women in this group progressed

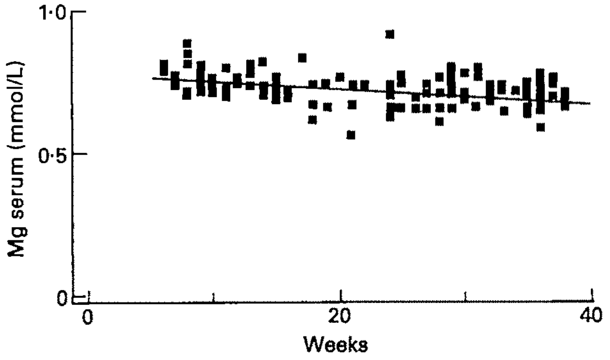


Fig. 1. Serum magnesium (Mg) concentrations in 71 normal pregnancies between 6 and 38 weeks gestation.

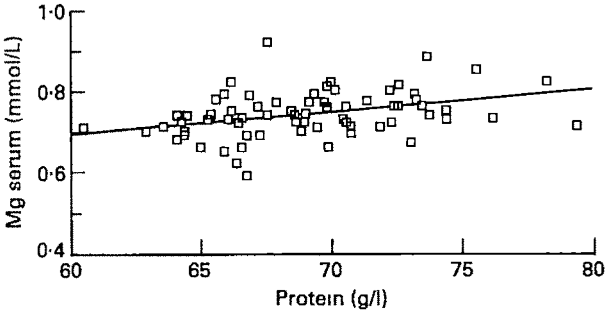


Fig. 2. Correlation between serum protein and magnesium concentrations in 71 normal pregnancies. r = 0·382, P = 0·001.

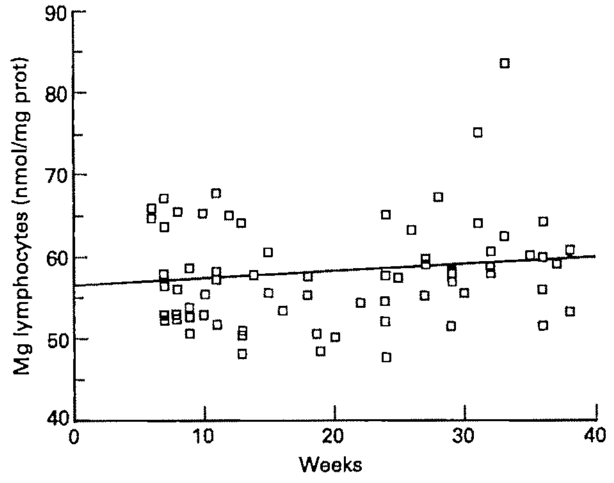


Fig. 3. Lymphocyte magnesium concentration in 71 normal pregnancies between 6 and 38 weeks gestation. r = 0·135, P = 0·26.

normally without development of hypertension. Fig 1 depicts the serum Mg concentration in these women showing a gradual, small but significant decrease during pregnancy (r = 0·384, P<0·001). There was a significant correlation (r = 0·382, P = 0·001)) between serum protein and Mg concentration (Fig. 2). Fig. 3 shows the intracellular lymphocyte Mg concentration (r = 0·135, P = 0·26).

Hypertensive groups and comparison group

Table 2 summarizes the mode of delivery and outcome in the three study groups. As expected, there were more instrumental vaginal deliveries and caesarean sections and more small-for-gestational age infants in the GH and PE groups.

Table 3 shows that serum concentrations of Mg were very similar in the normotensive comparison and GH groups but significantly higher (P<0·01) in the PE group. In contrast, the Mg concentration within the lymphocytes was similar in all three groups. Likewise, the urinary Mg excretion did not differ significantly between the three groups.

In the five patients treated with parenteral $MgSO_4$ a large increase in the serum Mg concentration and of the urinary Mg excretion was observed. However, the intralymphocytic Mg concentration remained remarkably stable (Fig. 4).

Discussion

In recent years there have been several studies of Mg metabolism during pregnancy and some have concluded that Mg deficiency might play a role in the aetiology of pre-eclampsia (Seelig 1980; Altura *et al* 1983; 1984; Conradt *et al.* 1984b; Günther 1985).

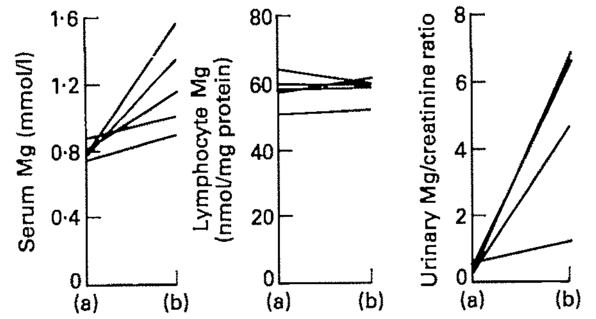


Fig. 4. Serum and lymphocyte Mg concentrations and urinary Mg excretion in five patients treated with $MgSO_4$ (a) before treatment with $MgSO_4$. (b) during treatment with $MgSO_4$.

The daily intake of Mg in the diet of pregnant women has been investigated and some studies have shown that the average total intake of Mg in pregnancy in the United States amounts to only 35%–60% of the recommended 450 mg (Ashe *et al* 1979; Franz 1987). This finding and the hypothesis that Mg deficiency could play a role in the pathogenesis of pre-eclampsia have led to controversy about whether Mg supplements should be prescribed during pregnancy. Some obstetricians routinely prescribe preparations containing from 10 to 20 mmol of Mg to be taken daily by pregnant women (Franz 1987; Conradt *et al.* 1984b).

In the first part of our study, we found a significant progressive reduction (P<0·001) in serum Mg concentrations during normal pregnancy (Fig. 1) as other studies have shown (Dancis 1971; Stanton 1987). The significant correlation (P<0·001) between the concentrations of Mg and proteins suggests that this decrease is partly due to haemodilution. The stability of intracellular Mg in the 71 healthy pregnant women is an argument against a state of Mg deficiency during normal pregnancy.

Animal studies (Altura *et al.* 1984) or studies of human umbilical vessels (Watson *et al* 1986) have shown that Mg is necessary to maintain a normal vascular tonus. Rats exposed to a poor Mg diet, or entirely without Mg, develop arterial hypertension. Mesenteric circulation in these animals diminishes in proportion to the Mg deficiency (Altura *et al* 1984). Pregnant ewes deprived of Mg during gestation develop a reduction in serum Mg accompanied by arterial hypertension, retarded intrauterine growth and pathological renal and placental changes similar to those of pre-eclampsia (Weaver 1986). The sudden fall in extracellular Mg produces a rapid increase in the tonus of umbilical arteries and veins taken from normal fetuses

Table 2. Mode of delivery and outcome in the three study groups

Mode of delivery	Gestational hypertension (n = 11) n (%)	Pre-eclampsia (n = 11) n (%)	Normotensive (n = 21) n (%)
Instrumental vaginal delivery	4 (36)	3 (27)	2 (10)
Caesarean section	2 (18)	6 (55)	1 (5)
Small for gestational age (<10th centile)	3 (27)	3 (27)	1* (5)

*At the 10th centile.

Table 3. Serum magnesium concentration, lymphocyte magnesium concentration and urinary magnesium excretion in the three study groups

	Gestational hypertension (n = 11)	Pre-eclampsia (n = 11)	Normotensive (n = 21)	P^1	P^2	P^3
Serum Mg (mmol/l)	0·684	0·778	0·704	0·176	0·008	0·005
Lymphocyte Mg (mmol/mg protein)	59·89	59·97	57·33	0·237	0·234	0·888
Urinary Mg (Mg/creatinine ratio)	0·42	0·45	0·35	0·272	0·538	0·888

P^1, normotensive *vs* gestational hypertension.
P^2, normotensive *vs* pre-eclampsia.
P^3, gestational hypertension *vs* pre-eclampsia.

(Altura 1983). Conversely, high dose of extracellular Mg (3 mmol/l) increase the production of vasodilating prostaglandin $F_{2\alpha}$ by endothelial cells in human umbilical veins (Watson *et al.* 1986).

We are not aware of any clinical study demonstrating that pregnant women with gestational hypertension or pre-eclampsia have a measurable Mg deficiency. Conradt *et al.* (1984b) suggested that gestational hypertension and pre-eclampsia are probably due to a Mg deficiency, they based their hypothesis on a retrospective study in which 2% of the women who had not received tocolytic drugs or Mg supplementation developed pre-eclampsia whereas none of the women who received tocolytic drugs and Mg supplementation developed gestational hypertension or pre-eclampsia. It should be noted that the women were not allocated on a random basis and there was no mention of measurement of either serum or intracellular Mg concentration. However, two prospective studies (Spätling & Spätling 1988; Sibaï *et al.* 1989) compared groups of pregnant women who received, respectively, 15 mmol and 365 mg Mg daily with control groups (who received no treatment) and found no significant difference in the occurrence of gestational hypertension and pre-eclampsia.

In our study the intralymphocytic Mg concentrations were similar in all three groups, in agreement with two other studies (Ryzen *et al.* 1987; Boston *et al.* 1989) which compared normal pregnant women with patients who had gestational hypertension or pre-eclampsia. We found that serum Mg concentrations were almost identical in the GH and normotensive groups and significantly higher in the PE group. We have no explanation for this difference. The urinary Mg excretion was not significantly different between the three groups. This is at variance with the report by Franz (1982) who found a significant negative correlation between urinary Mg excretion and the mean increase in arterial pressure in pregnant women with urinary Mg excretion less than 7 meq/g of creatinine. Finally, the stability of the intralymphocytic Mg concentrations in patients treated with high doses of intravenous $MgSO_4$ represents a powerful argument against the hypothetical deficiency of Mg in pre-eclamptic patients.

$MgSO_4$, given in high doses, is considered by some to be the first choice for treatment of severe pre-eclampsia and eclampsia (Pritchard *et al.* 1985; Lindheimer & Katz 1986) but its mode of action is not well understood and Pritchard does not consider it an effective treatment of the hypertension in pre-eclampsia. Our data do not support the hypothesis that Mg deficiency is a contributing cause of pre-eclampsia.

Acknowledgments

The authors gratefully acknowledge the excellent technical assistance of Marguerite Wyss and Laurence Aubert. The help of the midwives Elisabeth Riggs, Eleonor Hickey, Geneviève Christin and Elsie Vitry is also appreciated. Finally, we thank Professor Walter Herrmann for his critical review of the article.

References

Altura B. M., Altura B. T. & Carella A. (1983) Magnesium deficiency-induced spasms of umbilical vessels: relation to pre-eclampsia, hypertension, growth retardation. *Science* **221**, 376-378.

Altura B. M., Altura B. T. & Gebrewald A (1984) Magnesium deficiency and hypertension: correlation between magnesium deficient diets and microcirculatory changes *in situ Science* **223**, 1315-1317.

Ashe J. R., Schofild F. A. & Gram M. R (1979) The retention of calcium, iron, phosphorus, and magnesium during pregnancy· the adequacy of prenatal diets with and without supplementation. *Am J Clin Nutr* 32, 286-291.

Boston J. L., Beauchene R. E. & Cruikshank D. P. (1989) Erythrocyte and plasma magnesium during teenage pregnancy: relationship with blood pressure and pregnancy-induced hypertension. *Obstet Gynecol* 73, 169-174.

Burrow B. N. & Ferris T. F. (1988) *Medical Complications During Pregnancy.* Third edn., W. B. Saunders Company, Philadelphia, p. 14.

Conradt A. (1984) Neurere Modellvorstellungen zur Pathogenese der Gestose unter besonderer Berucksichtigung eines Magnesium-Mangels. *Z Geburtshilfe Perinat* **188**, 49-58.

Conradt A., Weidinger H. & Algayer H. (1984a) On the role of magnesium in fetal hypotrophy, pregnancy induced hypertension and pre-eclampsia. *Magnesium Bull* **6**, 68-76.

Conradt A., Weidinger H & Algayer H. (1984b) Reduzierte Frequenz von Gestosen bei Betamimetika-behandelten Risikoschwangerschaften mit Magnesium-Zusatz-Therapie. *Geburtshilfe Frauenheilk* **44**, 118-123.

Dancis J., Springer D. & Cohlan S Q. (1971) Fetal homeostasis in maternal malnutrition. II Magnesium deprivation. *Pediat Res* **5**, 131.

Elin R. J. & Johnson E. (1982) A method for determination of the magnesium content of blood mononuclear cells. *Magnesium* **1**, 115-122.

Franz A. B. (1982) Correlation of urinary magnesium excretion with blood pressure of pregnancy. *Magnesium Bull* **1**, 73-78.

Franz A. B. (1987) Magnesium intake during pregnancy. *Magnesium* **6**, 18-27.

Girardin E. & Paunier L. (1985) Relationship between magnesium, potassium and sodium concentrations in lymphocytes and erythrocytes from normal subjects. *Magnesium* **4**, 188-192.

Gunther T. (1985) The possible role of magnesium and zinc deficiency in the development of EPH-gestosis. *Magnesium Bull* **7**, 87-90.

Lindheimer M. D. & Katz A. I. (1986) The kidney in pregnancy. In *Pathogenesis of Renal Disease The Kidney.* Third edn. (Brenner B. M. & Rector F. C., eds), pp. 1253-1295.

Pritchard J. A., MacDonald P. C. & Gant N. F. (1985) *Williams Obstetrics* 17th edn. Appleton-Century Crofts, Norwalk, CT, pp. 539 and 547-548.

Ryzen E., Greenspoon J. S., Diesfield P *et al.* (1987) Blood mononuclear cell magnesium in normal pregnancy and pre-eclampsia. *J Am Coll Nutr* **6,** 121-124.

Seelig M. S (1980) The role of magnesium in normal and abnormal pregnancy. In *Magnesium Deficiency in the Pathogenesis of Disease* Plenum Press, New York. pp. 29-47.

Sibai B. M , Villar M. A. & Bray E. (1989) Magnesium supplementation during pregnancy: a double blind randomized controlled clinical trial. *Am J Obstet Gynecol* **161,** 115-119.

Spatling L. & Spatling G. (1988) Magnesium supplementation in pre-eclampsia. A double blind study. *Br J Obstet Gynaecol* **95,** 120-125

Stanton M F. & Lowenstein F. W. (1987) Serum magnesium in women during pregnancy while taking contraceptives and after menopause. *J Am Coll Nutr* **6,** 313-319.

Watson A. V., Moldow C F., Ogburn P. L., *et al.* (1986) Magnesium sulfate: rationale for its use in pre-eclampsia *Proc Natl Acad Sci USA* **83,** 1075-1078.

Weaver H. (1986) Pregnancy induced hypertension and low birthweight in magnesium deficient ewes. *Magnesium* **5,** 191-200.

Weidinger H. (ed) (1983) Magnesium und Schwangerschaft. In *Magnesium und Schwangerschaft,* Beltz, Weinheim, Basel, pp. 13-20.

Received 17 January 1990
Resubmitted 28 May 1991
Accepted 24 September 1991

British Journal of Obstetrics and Gynaecology
March 1992, Vol. 99, pp. 212–215

FETAL AND NEONATAL MEDICINE

The effects of fetal exposure to danazol

PETER J. BRUNSKILL

Consultant Obstetrician and Gynaecologist

Airedale General Hospital, Keighley
W. Yorks BD20 6TD, UK

ABSTRACT

Objective To assess the consequences of exposure to danazol *in utero*. Additionally, by assessing the risk, to facilitate the counselling of pregnant women inadvertently exposed to danazol in early pregnancy.
Design Retrospective review of reported case histories.
Subjects 129 women exposed to danazol during pregnancy were identified from individual case reports, data from the Australian Drug Reactions Advisory Committee and the United States Food and Drug Administration and from the reports of danazol exposure made directly to the manufacturers.
Main outcome measures Teratogenic effects of fetal exposure to danazol in relation to dosage and duration of exposure.
Results Of the 129 reported pregnancies, 12 miscarried and 23 were aborted. Of the 94 completed pregnancies, 37 resulted in the birth of normal males, 34 in non-virilized females and 23 in virilized females. Virilization occurred in a proportion of female fetuses with a pattern of cliteromegaly, fused labia and urogenital sinus formation. Surgery to the genital tract was usually, but not always, required in childhood. The abnormality has not been reported where danazol therapy had been discontinued before the 8th week of pregnancy. Although more common in the higher dosages, virilization was reported in one case with a 200 mg daily dosage.
Conclusions Danazol should remain contraindicated in pregnancy and clinicians should give careful contraceptive advice to patients commencing or continuing danazol therapy. Nonetheless it is possible to be cautiously optimistic about the outcome of danazol-exposed pregnancies, particularly if treatment is discontinued before 8 completed weeks gestation.

Despite the increasing availability of other medical therapies, danazol has retained an almost unique position in the management of endometriosis, and is also indicated for benign breast disease, menorrhagia and premenstrual syndrome (*Data Sheet*). It is therefore prescribed to women with reproductive potential by clinicians from a range of disciplines. Like many other drugs, danazol is contraindicated in pregnancy, but clinicians need to know the theoretical and actual risks to a fetus conceived during treatment with danazol or exposed to this drug after conception in order to offer advice and support to the pregnant woman.

A number of cases of danazol exposure in pregnancy have been published or reported to the manufacturers, and these are reviewed in this paper.

Pharmacology of danazol

Danazol is the 2,3, α-isoxazole derivative of 17 α-ethinyl testosterone (ethisterone). It is an androgen with antigonadotrophic and androgenic properties (Barbieri & Ryan 1981). It binds to androgen receptors producing androgenic effects (Chamness *et al.* 1980). It can also bind to progesterone receptors and this together with the androgen binding is probably responsible for its antigonadotrophic action (Riley 1990). However, danazol also exerts a direct inhibitory effect on steroidogenesis in the liver, adrenals and gonads (Barbieri *et al.* 1977) resulting in decreased circulating levels of oestrogen and progesterone, and it binds to and reduces circulating levels of sex hormone binding globulin (Chamness *et al.* 1980). This, along with the partial inhibition of adrenal hydroxylase enzymes (Stillman *et al.* 1980), leads to an increase in circulating levels of free androgens and probably explains the endometrial suppression which makes danazol the drug of choice in the medical treatment of endometriosis (Riley 1990). The relative androgen excess also explains the androgenic side effects often experienced by women on higher dosages of danazol: 15% develop acne and up to 5% report increased skin oiliness, weight gain, deepening of the voice or increased sexual hair (Duck & Katayama 1981). Danazol may also bind to glucocorticoid receptors (Barbieri *et al.* 1979), and there is evidence that it may modify the immune response by reducing the elevated levels of autoantibodies in women with endometriosis (El Roeiy *et al.* 1988).

Reports of exposure to danazol in pregnancy

Seven single case reports of danazol exposure in pregnancy

Correspondence: Peter J. Brunskill.

Table 1. Summary of reports of danazol exposure to US Food and Drug Administration (FDA) (after Rosa 1984)

	n
Miscarriages	7
Outcome unknown	14
Completed pregnancies	22
Normal males	7
Normal females	5
Virilized females	10
Total	43

have been published (Duck & Katayama 1981; Castro Magana *et al.* 1981; Schwartz 1982; Peress *et al.* 1982; Shaw & Farquhar 1984; Kingsbury 1985; Quagliarello & Alba Greco 1985). In addition, the Australian Drug Reactions Advisory Committee (ADRAC) reported four cases of fetal virilization (ADRAC 1986, 1989), one of which was also reported by Kingsbury (1985) and the United States Food and Drug Administration (FDA) reported 44 cases of danazol exposure in pregnancy (Rosa 1984) resulting in 22 live births. The FDA series included several of the individual case reports (Duck & Katayama 1981; Castro Magana *et al.* 1981; Schwartz 1982; Peress *et al.* 1982).

Six of the single case reports were female fetuses born between 27 weeks and term, the other one was a female fetus that was examined following a termination of pregnancy at 20 weeks (Quagliarello & Alba Greco 1985). In most cases danazol had been administered in dosages of 800 mg daily from early pregnancy until at least 14 weeks, although in one (Shaw & Farquhar 1984) a dose of 400 mg daily had been used. In each the indication for danazol therapy was endometriosis. Maternal virilization was not reported.

The abnormality reported in each case was a form of pseudo-hermaphroditism consisting of cliteromegaly, fused labia and a urogenital sinus opening at the base of the clitoris. In the case where the pregnancy was terminated at 20 weeks (Quagliarello & Alba Greco 1985), fetal necropsy revealed normal female external genitalia but a single opening in the vulva and a persistent urogenital sinus with the vaginal canal opening into the posterior urethra. In the case reported by Peress (1982), neonatal surgery was required for a hydrometrocolpos and in the case reported by Castro Magana *et al.* (1981) bilateral inguinal hernias were present. In two reports (Castro Magana *et al.* 1981; Schwartz 1982) endocrine investigations suggested the adrenogenital syndrome with a block in cortisol synthesis. In both cases the abnormality was transient but necessitated the administration of a single dose of corticosteroids.

Table 2. Outcome of pregnancies complicated by danazol exposure (manufacturer's data)

Miscarriages	12
Terminations	23
Completed pregnancies	94
Normal males	37
Non virilized females	34
Virilized females	23
Total	129

The ADRAC data include two reports of virilization with the presence of a urogenital sinus; in the other two cases no details are given The FDA analysis (Rosa 1984) of 44 cases comprises 36 notified to the manufacturers and 8 notified directly to the FDA. All the women had been taking danazol 800 mg daily and it was surmised that in each case treatment had begun after conception. The outcome of 43 of the 44 pregnancies is given in this report and summarised in Table 1. The author observed that these cases are not a representative sample of experience as many normal outcomes would not be reported. Virilization was not reported where danazol therapy had been discontinued before 7 completed weeks gestation.

Sterling-Winthrop Laboratories have received reports of 129 pregnant women exposed to danazol between 1975 and 1990. This series includes all reports from the UK and overseas and the published cases outlined above. The outcome of pregnancies in this series is summarized in Table 2.

In 23 of the 129 cases the pregnancy was terminated. The indications for termination (where known) are summarized in Table 3.

In these 129 pregnancies known to the manufacturer, information on the duration of danazol therapy was available for 36 pregnancies resulting in a female child; 15 in which there was virilization and 21 in which there was not. Fourteen out of the 15 cases of virilization were associated with exposure from the first week of pregnancy, compared with 13 of the 21 cases without virilization. Virilization was associated with a significantly longer period of exposure to a later stage in pregnancy. The minimum duration of exposure in a virilized fetus was 9 weeks. However, exposure up to 16 weeks was tolerated by some fetuses without virilization.

Information on dosage was available for 39 pregnancies resulting in a female child; 17 of these were virilized and 22 were not. Virilization was associated with higher dosages of danazol; however, although dosages under 400 mg daily may carry a lower risk, virilization was observed with 200 mg daily in one case.

In addition, the series of 129 cases known to the manufacturer contains two cases of congenital malformation other than virilization, three chromosomal abnormalities and three accounts of unspecified abnormality at birth or in later development. Although this represents considerable additional morbidity, no consistent pattern of these other abnormalities was found to indicate a causal relation with danazol. It should be noted that the review is based on reports without an appropriate control group.

Discussion

Non-adrenal fetal pseudohermaphroditism was first described

Table 3. Indications for termination of pregnancies exposed to danazol (manufacturer's data)

Concern about effects of danazol	7
Other reason (specified)	4
Other reason (not specified)	12
Total	23

Table 4. Duration of exposure and dosage of danazol in pregnancies resulting in female infants (manufacturer's data)

Variable	Non-virilized females Mean (SD) range	Virilized females Mean (SD) range	*P* value*
No. of pregnancies†	21	15	
Gestation (weeks)			
At start of danazol	2·3 (3·5) 0–12	0·9 (2·8) 0–11	<0·001
At end of danazol	7·2 (4·3) 0–16	16.7 (3·6) 12–24	<0·001
Duration of treatment (weeks)	5·0 (4·0) 0–16	15·9 (4·0) 9–24	<0·001
Daily dosage of danazol (mg)			
200	6	1	<0·001
300	3	0	
400	5	6	
600	2	2	
800	6	8	
No. of pregnancies†	22	17	

*Wilcoxon's 2-sample test (unpaired)

†Data on dosage alone were known for 39 pregnancies whereas details for duration of treatment were known for only 36 of them.

by Wilkins *et al.* (1958) following the use of certain oral progestogens in early pregnancy, but experimental data to support such a link have been available since 1942 (Courrier & Jost 1942. Other studies suggested that virilization was more likely if fetuses were exposed to the drug up to 12 weeks gestation (18%) (Jacobson 1962) than if exposure was only up to 8 weeks gestation (0·3%) (Bongiovanni & McPadden 1960). As the mechanism of virilization with danazol is similar, it is likely that discontinuation of danazol therapy before 8 weeks gestation would avoid virilization of a female fetus; this contention is supported both by the manufacturers data and the FDA report (Rosa 1984). Where danazol exposure has been prolonged and has extended beyond 8 weeks gestation, virilization may occur and in notified cases of exposure the rate of occurrence amounts to nearly 50% of female fetuses. It is likely, however, that the true rate of occurrence is much less than this as many cases with a normal outcome would not be reported.

In the affected female offspring surgery may be required to divide fused labia. However, in at least one affected infant with a urogenital sinus a normal vagina and urethra were demonstrated subsequently at 21 months of age (Kingsbury 1985). It seems reasonable therefore to delay surgical correction of the urogenital sinus until later childhood.

One long-term follow-up study of adult women exposed *in utero* to androgenic agents (Money & Matthews 1982) suggests that there are no adverse effects on sexual brain differentiation, spontaneous feminization occurring normally and at the correct time.

Danazol should clearly remain contra-indicated in pregnancy. Clinicians should instruct their patients to start treatment immediately after a normal menstrual period and to use barrier or other non-hormonal contraception (Rosa 1984; Quagliarello & Alba Greco 1985). Even the use of lower dosages of danazol (200–400 mg daily) can be associated with fetal virilization (manufacturer's data) and as these dosage levels may not suppress ovulation (US Physicians Desk Ref 1983) contraceptive advice is particularly important.

Treatment should be carefully supervised and discontinued before 8 weeks gestation if pregnancy does occur, to reduce the risk to the fetus. However, even if exposure to danazol is prolonged beyond 8 weeks gestation it is possible to be cautiously optimistic about the outcome of the pregnancy. Abnormalities when they occur seem to be relatively minor and amenable to surgery in childhood. No long-term morbidity has been reported in these infants. It would seem that the fetal risks do not, in general, constitute an overwhelming case for termination of pregnancy in the absence of other considerations.

More accurate assessment of the fetal risk is impossible at present because reporting is almost exclusively limited to the occurrence of adverse reactions. Many clinicians would welcome a reporting system for normal outcomes as well as adverse reactions. All cases of danazol exposure in pregnancy should be reported through the currently available channels even when the outcome is favourable.

Acknowledgments

I would like to thank Mrs N. Herbert RGN, Medical Information Officer to Sterling-Winthrop Group Ltd., for supplying and updating the manufacturer's data.

References

ADRAC (1986) Protecting the fetus: danazol masculinization. *Aust Adverse Drug React Bull*, April, Abstract no 1.

ADRAC (1989) Danazol masculinization—a reminder. *Aust Adverse Drug React Bull*, Nov, Abstract no 1.

Barbieri R. L., Canick J A., Makris A. *et al.* (1977) Danazol inhibits steroidogenesis. *Fertil Steril* **28**, 809-813

Barbieri R. L., Lee H & Ryan K. J. (1979) Danazol binding to rat androgen. glucocorticoid, progesterone and oestrogen receptors: correlation with biological activity. *Fertil Steril* **31**, 182-186.

Barbieri R. L. & Ryan K. J. (1981) Danazol-endocrine pharmacology and therapeutic applications. *Am J Obstet Gynecol* **141,** 453

Bongiovanni A. M. & McPadden A. J. (1960) Steroids during pregnancy and possible fetal consequences. *Fertil Steril* **11,** 181.

Castro-Magana M., Cheruvanky T., Collip P. J. *et al.* (1981) Transient adrenogenital syndrome due to exposure to danazol in utero. *Am J Dis Child* **135,** 1032-1034.

Chamness G. C. Asch R. H. & Pauerstein C. J. (1980) Danazol binding and translocation of steroid receptors *Am J Obstet Gynecol* **136,** 426.

Courrier R & Jost A. (1942) Intersexualite foetal movoquee sar la pregneninolone au cors de la grosesse. *CR Soc Biologie* **136,** 395.

Duck S. C. & Katayama K. P. (1981) Danazol may cause female pseudohermaphroditism. *Fertil Steril* **35,** 230-231.

El-Roeiy A., Dmowski W. P., Gleicher N. *et al.* (1988) Danazol but not gonadotrophin releasing hormone agonist suppresses autoantibodies in endometriosis. *Fertil Steril* **50,** 864-871.

Jacobson B. D. (1962) Hazards of norethidione therapy during pregnancy. *Am J Obstet Gynecol* **84,** 962.

Kingsbury A C. (1985) Danazol and fetal masculinization: a warning. *Med J Aust* **143,** 410-411.

Money J. & Matthews D (1982) Prenatal exposure to virilizing progestins: an adult follow-up study of twelve women. *Arch Sex Behav* **11,** 73–83.

Peress M. R., Kreutner A. K, Mathur R. S. & Williamson H. O. (1982) Female pseudohermaphroditism with somatic chromosomal anomaly in association with in utero exposure to danazol. *Am J Obstet Gynecol* **142,** 708-709.

Quagliarello J & Alba Greco M. (1985) Danazol and urogenital sinus formation in pregnancy. *Fertil Steril* **43,** 939-942.

Riley A J. (1990) Danazol offers more than ovarian suppression *Brit J Sex Med* **17,** 7-9.

Rosa F W. (1984) Virilisation of the female fetus with maternal danazol exposure. *Am J Obstet Gynecol* **149,** 99-100.

Schwartz R P (1982) Ambiguous genitalia in a term female infant due to exposure to danazol in utero *Am J Dis Child* **136(5),** 474.

Shaw R. W. & Farquhar J. W. (1984) Female pseudohermaphroditism associated with danazol exposure *in utero.* Case Report. *Br J Obstet Gynaecol* **91,** 386–389.

Stillman R. J., Monserrat De M. F., Schiff I., Barbieri R. L. & Tulchinski D. (1980). Inhibition of adrenal steroidogenesis by danazol in vitro. *Fertil Steril* **33,** 401.

US Physicians Desk Reference (1983) (37th edition), 2126-2127.

Wilkins L., Jones H. W, Holman G H & Stempfeld R. S. (1958) Masculinization of the female fetus associated with administration of oral and intramuscular progestins during gestation: nonadrenal female pseudo-hermaphroditism. *J Clin Endocrinol Metab* **18,** 559-585.

Received 9 October 1990
Resubmitted 24 July 1991
Accepted 14 October 1991

British Journal of Obstetrics and Gynaecology
March 1992, Vol. 99, pp. 216–219

FETAL AND NEONATAL MEDICINE

A tale of two prior probabilities—avoiding the false positive antenatal diagnosis of autosomal recessive polycystic kidney disease

R. J. LILFORD
Department of Obstetrics and Gynaecology
H. C. IRVING
Department of Radiology
E. B. ALLIBONE
Department of Histopathology

St James's University Hospital, Leeds
LS9 7TF

ABSTRACT

We describe a case in which the typical ultrasound diagnosis of infantile polycystic kidney in a woman with no family history of renal disease was not confirmed by histology following termination of the pregnancy. This is contrasted with the situation in another couple who were known carriers of autosomal recessive polycystic kidney disease and where the prenatal ultrasound diagnosis was confirmed histologically. When prior genetic risk is low, the possibility of a normal or less severe outcome must be discussed with parents when fetal ultrasound shows large, echogenic kidneys but normal amniotic fluid volume.

Bayesian mathematicians know that the likelihood of a disease, given certain signs and symptoms, is very strongly influenced by its prevalence (prior probability). Intuitive diagnosticians try to capture this concept in the old adage 'common things occur commonly'. The ratio of false to true positive results of any test declines as prevalence falls. This may result in the tragic termination of wanted pregnancies when low-risk pregnancies are screened for fetal anomalies. In this paper we describe, for the first time, the apparent false-positive diagnosis of autosomal recessive polycystic kidney disease (ARPKD) in a pregnant woman with a negative genetic history (and therefore low prior probability). This is contrasted with the correct diagnosis of this condition in the fetus of known carrier parents on the basis of similar but less extreme ultrasound appearances.

Clinical description

The first woman was referred to the prenatal diagnostic clinic because of the previous loss of a baby with histologically confirmed ARPKD (Potter type I). A fetal anomaly scan at 19 weeks gestation showed hyperechogenic, albeit normal sized, kidneys (Fig. 1a). Amniotic fluid volumes were completely normal. A diagnosis of a further fetus with ARPKD was made and the pregnancy was terminated. Histological examination of the fetal kidneys (Fig. 1b) and of the liver (Fig. 1c) confirmed the diagnosis. This woman has subsequently embarked upon a further pregnancy and has a normal child.

The second case concerns a normotensive primigravid woman with no family history of single gene disease, whose fetus was found to have hyperechogenic kidneys during a routine ultrasound scan at 18 weeks gestation. Amniotic fluid volumes were completely normal. A subsequent scan at 19 weeks gestation showed hyperechogenic and large fetal kidneys (Fig. 2a). A confident diagnosis of ARPKD was made and the prognosis of this disease, including the poor results of renal transplantation in infancy, was discussed with the parents. The parents elected to undergo termination of pregnancy. The fetus was normal on postmortem examination.

Histological examination of the kidneys (Fig. 2b) and liver (Fig. 2c) failed to confirm the antenatal diagnosis. These findings were checked by a pathologist with special interest in renal cystic diseases, Professor Risdon, of the Hospital for Sick Children, Great Ormond Street. It has not been possible to obtain renal ultrasound scans on both parents.

Discussion

The ultrasonic 'texture' of fetal kidney is normally very similar to that of lung. ARPKD is associated with hyperechogenic 'bright' kidneys, which are also usually enlarged (Boal & Teel 1980). The condition is frequently but not always detectable antenatally (Luthy & Hirsch 1985). The kidneys in the first case, conformed with the first of these criteria and against the background of a 25% prior probability, termination of pregnancy was recommended confidently. In our second case, the ultrasonic features appeared even more clearcut, since the kidneys were both hyperechogenic and enlarged. Fig. 2 shows an appearance that is almost identical to that demonstrated by Campbell & Pearce in their classic monograph (1983). This is quite unlike the ultrasound appearance of normal kidney (Fig. 3).

When the histology report failed to confirm our confident antenatal diagnosis we discussed the case with colleagues interested in prenatal diagnosis. We found that we were not the first to encounter a pregnancy where histological examination after termination of pregnancy had failed to confirm the antenatal diagnosis and one expert comforted himself with the idea that ultrasound may be more sensitive than histology or, to put it more bluntly, that the histological diagnosis was wrong. Bio-

Correspondence: Professor R. J. Lilford.

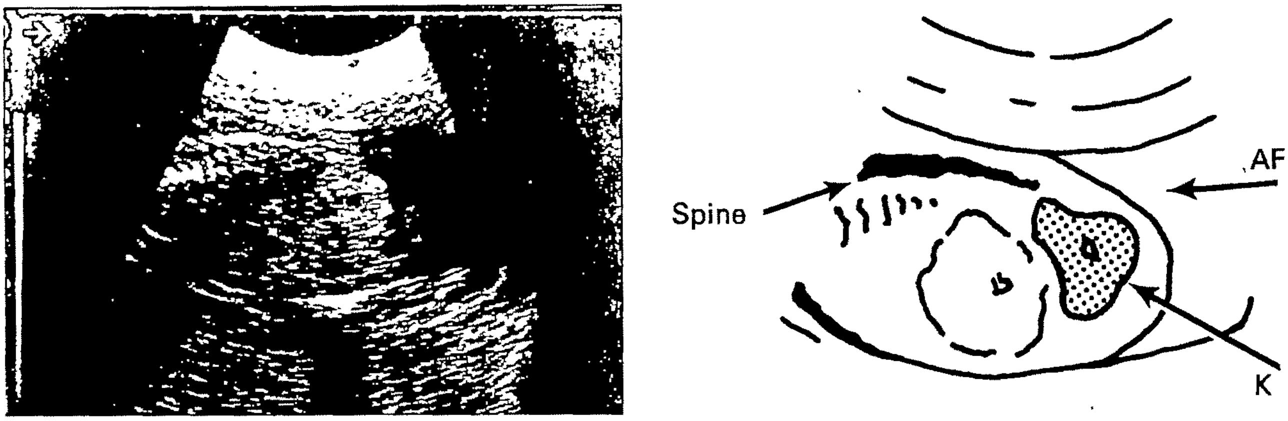


Fig 1a. Oblique view of the upper abdomen at 19 weeks gestation showing hyperechogenic kidneys which were, however, not enlarged at this stage of gestation. AF = amniotic fluid, K = hyperechogenic kidney.

logical function is the gold-standard against which all other diagnostic methods, including histology, should be measured. Nevertheless, in the absence of clinical outcome data, we are inclined to give greater weight to histological findings than to ultrasound appearance, i.e. we think it more likely that it was the ultrasound, rather than histology, which gave a false diagnosis in this case. Considerable experience with normal and abnormal hepatic and renal histology from mid-trimester fetuses has been accumulated. Specific hepatic and renal lesions have always been found on microscopy in pregnancies terminated at this gestational age on the basis of both ultrasound and a positive genetic history (both in our experience and that of Risdon, personal communication). The lesion in classical infantile polycystic kidney disease is lethal unless treated by transplantation. We think that the subjective probability of this lethal disease offered to low risk parents, when features of ARPKD are detected, should be lower than the 99% risk offered to our patient. Nevertheless, some couples may request termination of pregnancy, even when the possibilities of normal outcome or later onset disease have been explained to them. Such couples may accept fetal liver biopsy since the risks, even of this invasive procedure, fall well short of the inevitability associated with termination. They would have to accept a possible sampling error, i.e. no portal tract included. However, we think that many couples at low prior risk, given the uncertainty of ultrasound diagnosis, would decline all further intervention and continue the pregnancy. The final outcome in these cases would provide probabilistic information for future women with positive ultrasound findings, but in whom genetic history is negative.

Starting from the premise that the second case described here was not affected with ARPKD, our experience emphasizes the importance of prior probability in clinical decision making. If we assume that the incidence of this condition is 2/100 000, as reported by Potter (1972), then only a very accurate (sensitive and specific) test will avoid a high proportion of false to true positive diagnoses. If the ultrasound test was 80%

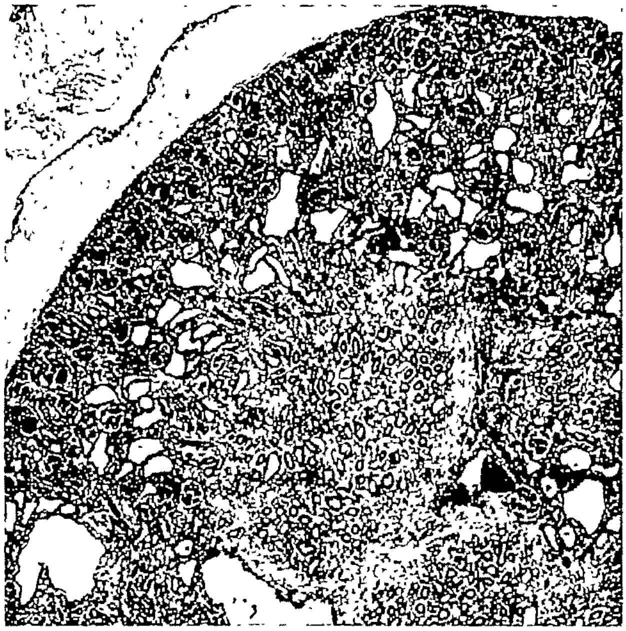


Fig. 1b. Section of kidney, following termination at 19 weeks gestation, showing normal architecture and nephroblastic zone but dilatation of numerous tubules in the deeper cortex and a normal medulla.

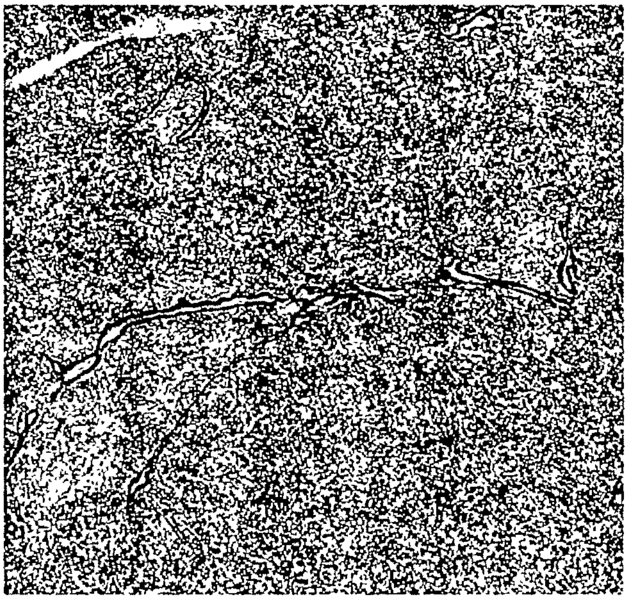


Fig. 1c. Section of liver, in the same patient as shown in Figs. 1a and b, showing angulated branching of the biliary ducts, with some cystic change, especially in the larger portal systems.

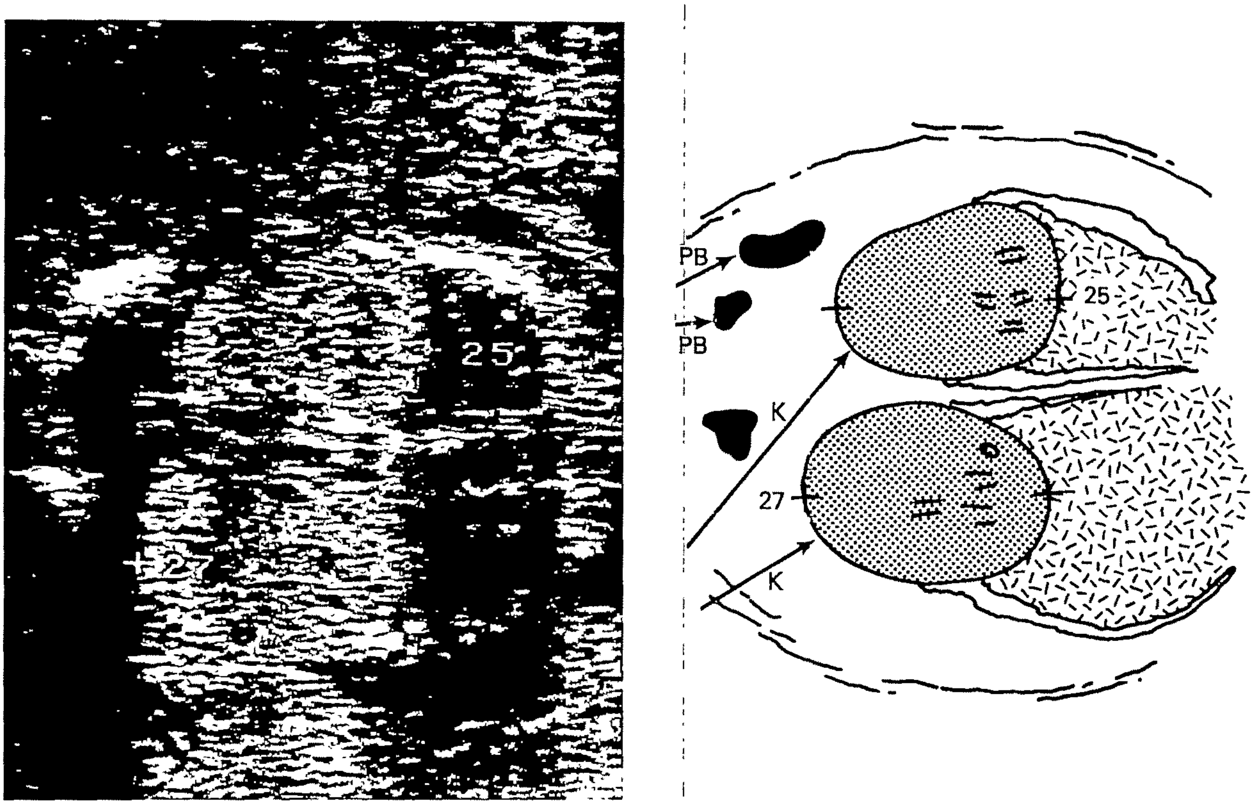


Fig. 2a. Coronal view of fetal kidney at 19 weeks gestation in the patient who ultimately turned out to have normal histology. PB = pelvic bones; K = hyper-echogenic kidneys in coronal section; L = lung.

sensitive, and highly specific with a false-positive rate (1–specificity) of 1 in 5000 then the probability of an affected fetus, given positive ultrasound findings, would be only 0·07 (7·4%). If we take more extreme values and assume that the test will identify 90% of affected fetuses, with a false-positive rate of only 1 in 10 000, then the probability that the fetus is affected, remains low at 0·15 (15%). Potter's estimate of the background incidence is low and Bosniak & Ambos (1975) estimate that about 1 in 10 000 births are affected. On these prior odds, the posterior probabilities under the above sensitivity and specificity assumptions are 0·28 and 0·47, respectively, which leaves plenty of scope for error. However, if we start from a prior probability of 0·25 (as one would in a couple who have had a previously affected child) then the probabilities that the disease is present are 0·999 and 0·99999 respectively for the two test accuracy assumptions specified above. Our estimation of incomplete sensitivity, especially at 20 weeks gestation, is in keeping with published reports. For example, Reuss *et al.* (1990) were able to detect five out of six pregnancies where infantile polycystic kidney disease recurred in high-risk mothers. The existence of a false-positive rate, albeit measured in the thousands, is supported not only by the patient reported

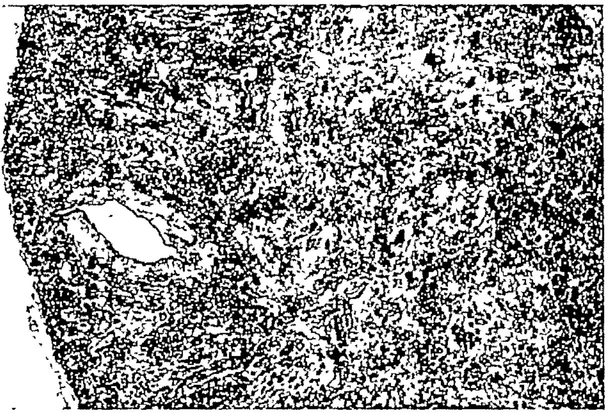


Fig. 2b. Histological section of kidney, following termination of pregnancy at 19 weeks gestation in a patient before scan is shown in Fig. 2a. The tubules are believed to be within normal limits; magnification 25.

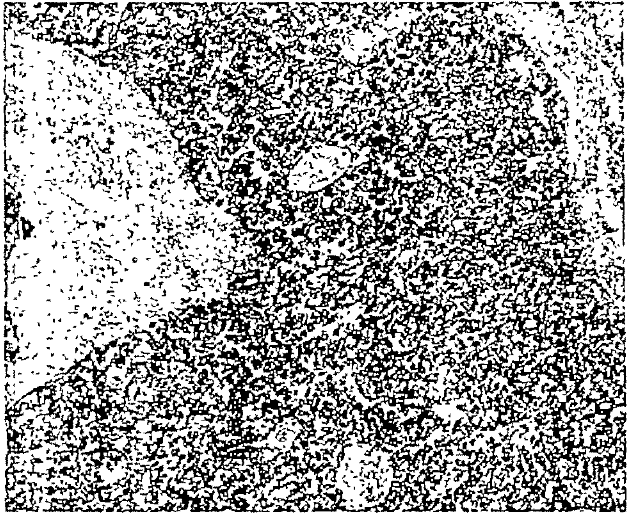


Fig. 2c. Section of the liver, from the same patient shown in Figs. 2a and b, showing completely normal portal systems.

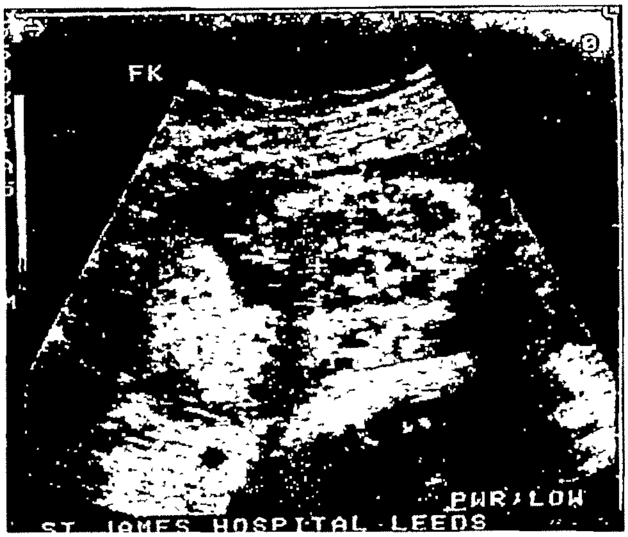


Fig. 3. Coronal ultrasound section of normal kidney (+——+) at 19 weeks gestational age

here, but also by informal contact with specialist colleagues. We suspect that there is a certain reluctance to publish such case reports and that the ultrasound literature is biased towards success rather than failure.

Nevertheless, we are still left with the puzzling observation, that the histology and ultrasound observations do not always agree. At least two explanations are possible. The first is that ultrasound has detected a milder form of kidney disease which does not manifest clearly abnormal histology at mid-gestation. This could be either a form fruste of ARPKD—the so-called juvenile form (Dalgaard 1957) or autosomal dominant ('adult') polycystic kidney disease. The latter condition may cause prenatal kidney enlargement (Edwards & Baldinger 1989) as early as 16 weeks gestation (Ceccherini *et al* 1989) although discreet cysts are typically seen (Romero *et al* 1988). Clinical or ultrasound evidence of the disease may be absent in the parents in such cases (Journel *et al.* 1989) because of new mutation or non-paternity, rather than low penetrance. The second explanation for disagreement between ultrasound and histology may lie in a minor and unimportant anatomical variation falling within the normal limits for the histology of the fetal kidney, for instance bilateral segmental renal dysplasia. Awareness of the possibility of false-positive results and follow-up of those fetuses where the parents elect to continue the pregnancy will improve our understanding of this problem. Parents could be made aware that if the child turns out to have a form of kidney disease less severe than classical ARPKD, then renal failure is unlikely before late childhood or adult life, when the prospects for transplanation are more favourable.

Acknowledgments

We thank Professor Risdon for sharing his knowledge of this subject with us and for reviewing histology in the second case described.

References

Boal D. K & Teel R. L. (1980) Sonography of infantile polycystic disease. *Am J Radiol* **135,** 575–580.

Bosniak M A. & Ambos M. A. (1975) Polycystic kidney disease. *Semin Roentgenol* **10,** 133–143.

Campbell S & Pearce J. M. (1983) The prenatal diagnosis of fetal structural anomalies by ultrasound. *Clin Obstet Gynaecol* **10,** 475–506.

Ceccherini I., Lituania M., Cordone M. S., *et al* (1989) Autosomal dominant polycystic kidney disease: prenatal diagnosis by DNA analysis and sonography at 14 weeks. *Prenat Diagn* **11,** 751–758.

Dalgaard O. Z (1957) Bilateral polycystic disease of the kidney. A follow-up of 285 patients and their families *Acta Med Scan* [Suppl], 328

Edwards O. P & Baldinger S. (1989) Prenatal onset of autosomal dominant polycystic kidney disease *Urology* **34,** 265–270

Journel H., Guyot C., Barc R. M., Belbeoch P., Quemener A. & Jouan H. (1989) Unexpected ultrasonographic prenatal diagnosis of autosomal dominant polycystic kidney disease. *Prenat Diagn* **9,** 663–671

Luthy D A. & Hirsh J. H. (1985) Infantile polycystic kidney disease: observations from attempts at prenatal diagnosis. *Am J Med Genet* **20,** 505–517.

Potter E. L. (1972) Type I cystic kidney: tubular giganticism in normal and abnormal development of the kidney: In *Chicago Year Book,* Year Book Medical Publishers, Chicago, pp. 141–153.

Reuss A , Wladimiroff J. W , Stewart P. A. & Niermeijer M F (1990) Prenatal diagnosis by ultrasound in pregnancies at risk for autosomal recessive polycystic kidney disease. *Ultrasound Med Biol* **16,** 355-359.

Romero R., Pilu G., Jeanty P., Ghidini A. & Hobbins J C. (1988) Adult polycystic kidney disease In *Prenatal Diagnosis of Congenital Anomalies* (Romero R., Pilu G , Jeanty P., Ghidini A. & Hobbins J. C , eds), Appleton & Lange, Norwalk, Connecticut, California, pp 268–270.

Received 18 April 1991
Accepted 7 October 1991

British Journal of Obstetrics and Gynaecology
March 1992, Vol 99, pp. 220–225

FETAL AND NEONATAL MEDICINE

Screening for congenital heart disease prenatally. Results of a 2½-year study in the South East Thames Region

GURLEEN K. SHARLAND
LINDSEY D. ALLAN

Department of Paediatric Cardiology
Guy's Hospital
London, UK

ABSTRACT

Objective To assess the efficacy of four chamber view examination, during routine obstetric scanning, in the prenatal detection of fetuses with congenital heart disease.
Design Prospective observational study.
Setting Ten obstetric ultrasound units in the South East Thames Region.
Subjects All pregnant women attending for routine obstetric ultrasound examination.
Intervention Ultrasonographers performing routine ultrasound examinations were taught to obtain, and correctly interpret, the four chamber view of the fetal heart. When this view could not be achieved adequately, an attempt was made to identify a reason for failure and, if possible, to arrange a repeat scan. All suspected abnormalities were referred to a specialized unit.
Main outcome measures Numbers of true abnormalities detected or overlooked, and the number in whom abnormality was suspected incorrectly.
Results Over a 2·5-year period, 69% of the known number of cardiac lesions associated with an abnormality of the four chamber view were detected prenatally during the routine obstetric scan, 10% were identified as a result of referal for other high-risk factors and 21% were overlooked. The overall positive predictive value in the 10 obstetric units was 36%.
Conclusions Prenatal screening for some forms of major congenital heart disease is possible by including examination of the four chamber view of the fetal heart in routine obstetric scans. However, there are important limiting factors that will influence the success of abnormality detection and must be taken into account if screening is to be effective nationwide.

Congenital malformation is one of the most common causes of mortality in childhood in England and Wales (Forfar 1984). Congenital heart disease is the commonest form of severe congenital abnormality and is associated with over half the deaths from congenital malformations in childhood (OPCS 1986; 1988). Normal cardiac anatomy can be defined in the fetus from 16–18 weeks gestation by ultrasound and an accurate diagnosis of structural cardiac malformations can therefore be predicted from this time (Kleinman *et al.* 1980; Allan *et al.* 1984). A detailed complete cardiac scan can usually only be performed in specialised centres with expertise in the diagnosis of congenital heart disease and high risk pregnancies (Sharland & Allan 1990) are referred to such units for fetal echocardiography. However, most children with heart disease are born to mothers who have no known high risk features during pregnancy (Cullen *et al.* 1990). The concept of prenatal screening for congenital heart disease in this country was therefore introduced, to improve the detection of these cases (Allan *et al.* 1986). The method involves teaching ultrasonographers to examine one section of the fetal heart, the four chamber view, on all routine obstetrics scans. In France, an effective screening programme has already been initiated (Fermont *et al.* 1985). A recent report from the North Regional fetal abnormality survey, however, suggested that the sensitivity for the antenatal detection of cardiac malformations was poor, as only 3 of 71 fetuses with congenital heart disease were detected prenatally (Members of Joint Group on Fetal Abnormalities 1989). This has not been the experience in our unit, where most abnormalities seen are referred after the detection of an abnormal four chamber view on routine scan. Staff in obstetric units all over the country have been taught to examine the four chamber view over the past 4–5 years. However, selection of these units has been arbitrary and determined mainly by the interest shown by the staff. Over the past 2·5 years, 10 obstetric units in the South East Thames Region have been taking part in a more formal screening programme, to assess the efficacy of four chamber view examination, during routine obstetric scanning, in the detection of congenital heart disease.

Correspondence: Dr G Sharland, Department of Paediatric Cardiology, 11th Floor, Guy's Tower, Guy's Hospital, St. Thomas Street, London SE1 9RT.

Methods

The four chamber view is obtained by imaging a transverse

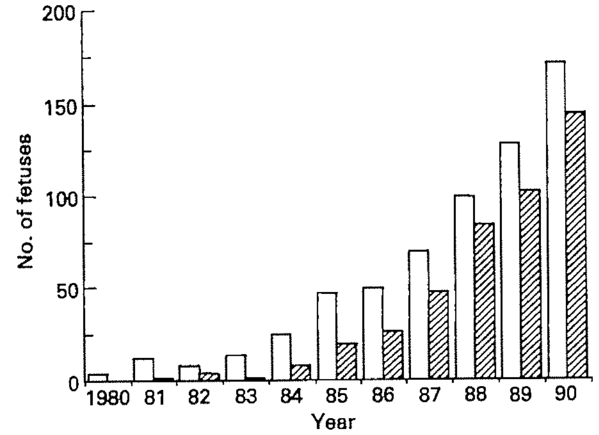


Fig. 1. The number of fetuses with congenital heart disease (CHD) referred because an abnormality of the four chamber view had been suspected on routine obstetric scanning compared with the total number of fetal cardiac abnormalities seen per annum. □ total abnormalities; ▨ suspected CHD.

section across the fetal thorax above the level of the diaphragm. The appearance of the four cardiac chambers can vary depending on the orientation of the ultrasound beam to the heart, but ultrasonographers are taught how to identify the different cardiac structures regardless of orientation (Allan *et al.* 1986) and then to check the following features: (1) the heart should not occupy more than one third of the fetal thorax; (2) there are two atria (left and right) which are of equal size; (3) there are two ventricles (left and right) which are of equal size and thickness, and also contract equally; (4) there are two atrioventricular valves (mitral valve on the left and tricuspid valve on the right) which meet the atrial and ventricular septa at the crux of the heart in an offset cross-appearance; (5) the foramen ovale defect is present in the atrial septum; (6) the ventricular septum appears intact.

Four chamber view scanning nationwide

Over the past 4–5 years, staff involved with obstetric ultrasound, scanning in hospitals throughout the country, have become familiar with the idea of four chamber view scanning, either as a result of hearing lectures on the topic or from a single on-site visit to their hospital. The only factor determining hospital selection for a visit was the level of interest shown by the staff. The level of expertise was therefore arbitrary. To assess the impact of four chamber view scanning resulting from this method of teaching, the number of fetuses with cardiac malformations referred to our unit because an abnormality had been suspected on a routine obstetric scan were examined. These were compared with the total number of abnormalities seen per year.

Screening programme in South East Thames Region

To examine the efficacy of four chamber view scanning more specifically, a formal screening programme was introduced in 10 obstetric units in the South East Thames Region. The units were selected by contacting both the consultant in charge and the senior radiographer. Those showing a positive response and an interest in taking part in the screening programme were included in the study. All the ultrasonographers involved in routine obstetric scanning were taught to obtain, recognise and interpret, the four chamber view of the fetal heart. When the four chambers were not seen, the ultrasonographers were asked to identify a reason for failure if possible. They were also encouraged to ask pregnant women in whom adequate pictures were not obtained, to return for a repeat scan. Any pregnancy with a suspected abnormality was referred to our unit for further assessment. The paediatricians in each unit were informed that the study was taking place, so that information regarding abnormalities overlooked prenatally could be obtained. The selected units were visited on a regular basis with a time interval between each visit of between 6 weeks and 3 months. Each of these units started the study at a different time, the first starting on April 1st 1988.

Results

The number of abnormalities identified by four chamber view screening as a proportion of the total number detected in our unit over the last 10 years is shown in Fig 1. The overall numbers referred as a suspected abnormality have increased steadily since the introduction of four chamber view scanning and, over the past 3 years, the proportion of abnormal fetuses

Table 1. The results of four chamber view screening in the 10 selected obstetric units in the South East Thames Region*

Unit	Months in study	Deliveries per year	Expected number	Nos. detected	Nos. missed	False positives
1	32	2269	12	12	1	32
2	29	1820	9	6	3	16
3	27	2441	11	8	1	8
4	25	2889	12	5	2	9
5	19	1802	6	5	1	5
6	14	2439	7	4	2	6
7	12	3300	7	4	3	6
8	11	3067	6	3	2	7
9	9	1956	3	3	N/K	4
10	9	1878	3	3	1	3
Total				53	16	96

*Additional eight fetal cardiac anomalies were detected in pregnancies referred for other reasons.
N/K = none known.

Table 2. Breakdown of the cardiac diagnosis in 53 fetuses with congenital heart disease detected by screening

Diagnosis	Number
Hypoplastic left heart syndrome	10
Atrioventricular septal defect	10
Critical aortic stenosis	5
Coarctation/Interrupted aortic arch	4
Mitral atresia	4
Ventricular septal defect, double outlet right ventricle	4
Ventricular septal defect	4
Pulmonary atresia, intact ventricular septum	2
Pulmonary atresia, ventricular septal defect	2
Double inlet ventricle	2
Tricuspid atresia	2
Aortic atresia, Ebstein's anomaly	1
Absent pulmonary valve with tetralogy of Fallot	1
Ebstein variant, ventricular septal defect	1
Cardiac tumour	1

who were referred for this reason has been 80–85% of the total number of cardiac defects detected. These referrals have been obtained from over 100 different hospitals throughout the country. Assessment of the numbers of cardiac abnormalities overlooked during this period was not possible, due to the number of units involved and the large geographical area covered.

Abnormalities detected from screening programme

Between 1980 and 1988 the 10 units selected for this study had referred only eight fetuses with cardiac abnormality suspected during routine scan for fetal echocardiography. In contrast, during the study period of 32 months, 53 fetuses with congenital heart disease were detected by four chamber view screening. The number of abnormalities detected in the 10 individual units are shown in Table 1. The expected number of abnormalities in Table 1 was calculated on the prediction that severe fetal cardiac malformation should be detectable on four chamber view examination only in 2/1000 pregnancies. The number of deliveries annually and the time since the start of the study have been taken into account here. A breakdown of the cardiac diagnoses is shown in Table 2. There were an additional eight fetal cardiac abnormalities detected prenatally in women booked at these units, but who were referred for other reasons: six because there was an extracardiac fetal abnormality, one with a family history of congenital heart disease and one because of maternal diabetes.

Table 3. Breakdown of the cardiac diagnosis in the 16 fetuses with congenital heart disease that were overlooked during the screening study

Diagnosis	Number
Hypoplastic left heart syndrome	5
Atrioventricular septal defect	5
Coarctation	3
Interrupted aortic arch	1
Critical aortic stenosis	1
Critical pulmonary stenosis	1

Missed abnormalities during study period

During the study period, there were 16 cardiac abnormalities, that were considered likely to be associated with an abnormal four chamber view in early pregnancy, but which were overlooked prenatally in the screening units. These are listed in Table 3 and the numbers missed in the individual units in Table 1. Abnormalities of the great arteries that were missed, since these are sometimes associated with a normal four chamber view, are excluded here. It is possible that there are some false negatives we have not identified, as not all cases of congenital heart disease present in the first few weeks of life, and babies may have been transferred to other hospitals without the knowledge of local paediatricians, but this is unlikely. Table 4 shows a list of abnormalities that were considered to be detectable on a four chamber view and Table 5 lists conditions that may be associated with a normal view.

The scan records of the 16 fetuses where congenital heart disease was not detected prenatally were examined retrospectively. In four, gross maternal obesity did not allow an adequate view of the fetal heart. In a further four, the gestational age was <18 weeks at the time of the scan and in three, the four chamber view had not been seen adequately because of an unsuitable fetal lie. In the remaining five, no specific difficulty had been reported and four chambers were apparently seen. In two of these five, the scan had been performed by a junior, relatively inexperienced, member of staff.

Sensitivity and specificity

Of the total number of known abnormalities detectable, 69% were identified as a result of screening, 10% were identified as a result of referral for other high-risk factors and only 21% were overlooked. The sensitivity of four chamber view screening for detecting cardiac lesions associated with an abnormal four chamber view during the study period was thus 77% (true positives/true positives + false negatives). During the study period there were 96 fetuses in whom a cardiac abnormality was suspected but the cardiac structure was found to be normal on a subsequent scan in our unit. The numbers in the individual

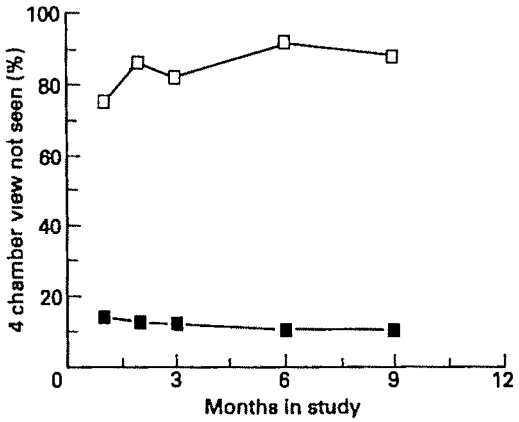


Fig. 2. The percentage of fetuses in whom the four chamber view of the fetal heart could not be seen at before or after 18 weeks gestation. The scans were performed by the same staff, in the same unit, using the same ultrasound imaging system. The results shown are from approximately 1360 pregnant women screened in Unit 2 during the first 9 months in the study. —□— <18 weeks; —■— >18 weeks.

Table 4. Cardiac anomalies usually associated with an abnormal four chamber view of the fetal heart

Mitral atresia	Critical pulmonary stenosis
Tricuspid atresia	Severe coarctation
Aortic atresia	Double inlet ventricle
Pulmonary atresia	Severe Ebstein's anomaly/tricuspid valve dysplasia
Atrioventricular septal defect	Large ventricular septal defect
Critical aortic stenosis	Unobstructed total anomalous pulmonary venous connection

units is shown in Table 1. These, therefore, represent false positives in terms of the initial screening. Since the total number of women with a normal fetus scanned during the study period was over 30 000, the specificity for screening in this study was over 99%. The positive predictive value of four chamber view screening in the 10 units combined was 36%. However, as indicated in Table 1, this varied in the individual units, and was 50% in three of the units. The number of false positives was related to the confidence and experience of the staff, rather than to the equipment being used.

Reasons for not obtaining four chamber view

The main factors recorded for not obtaining a four chamber view were maternal obesity, difficult fetal lie, a gestational age of less than 18 weeks, and equipment giving poor resolution.

The influence of gestational age on depicting the four chambers was demonstrated by Unit 2. Pregnant women in this unit had their routine scans at 16 weeks gestation at the start of the study, although some scans were performed after this time. The four chambers could not be seen adequately in most fetuses examined before 18 weeks gestation, whereas scanning after this time improved identification considerably (Fig. 2). Two of the abnormalities missed by this unit were during examinations before 16 weeks gestation. As a result, 10 months after the start of the study, the timing of the routine scan was changed to 18 weeks.

The equipment was different in each of the units and the resolution available affected the percentage of fetuses in whom the four chambers could be seen. In Unit 3, the same staff were using two machines which provided images of different quality. Machine 1 (Picker LSC 7000–2) had both a 5 MHz and 3·5 MHz transducer and provided higher resolution images compared to machine 2 (Picker LS 5000), which only had a 3·5 MHz transducer. The percentage of fetuses in whom the four chambers could not be identified for the two machines is shown in Fig. 3. It can be seen that the four chamber view could be identified in a larger proportion using machine 1 than machine 2.

Recall rate

The percentage of fetuses in whom a four chamber view could not be seen varied greatly in the different units at the start of the study However, this improved with time, as is illustrated by the first four units, all of whom have been in the study for over 2 years (Fig. 4). During the 2-year period, the percentage in whom four chambers could not be seen on the first attempt gradually fell. This trend was also observed in the other six units, so that by the end of the study, all 10 units reported identification of the four chamber view in at least 85–90% of fetuses on the first attempt, the percentage being higher in the units that had been in the study longer. The rate of recalling pregnant women in whom four chambers had not been seen in the fetus, thus also changed with time. As the proportion in whom an adequate view was achieved increased, the total number needing to be recalled decreased so that it became increasingly feasible to recall those in whom the four chamber view had been inadequately seen. Thus, the final percentage in whom four chambers could not be seen was less than 5% in most units.

Outcome

The outcome of the 53 fetuses with cardiac abnormality detected as a result of the screening programme is shown in Table 6. Overall 45 were detected at a gestation at which termination of pregnancy was an option, and 36 of the 45 pregnant women (80%) chose this course. Of the remaining fetuses, spontaneous intrauterine death occurred in four and nine babies died postnatally. There are four survivors, all with major heart disease.

Discussion

Congenital malformations remain one of the major causes of perinatal and infant mortality in developed countries. The Helsinki Ultrasound Trial recently examined the effect of screening all pregnant women with ultrasound in a population where the perinatal mortality is already very low (Saari-Kemppainen *et al.* 1990). The main cause of perinatal mortality in this population is major congenital malformation. This study showed that the perinatal mortality in a screened group was significantly lower than in a control group, the difference being due to the detection of major fetal anomalies by ultrasound screening and subsequent termination of pregnancy. The results of our study show that screening for some of the major forms of congenital heart disease can be implemented prenatally by those performing the routine obstetric scan if the four chamber view of the fetal heart is examined correctly. This

Table 5. Cardiac anomalies usually associated with a normal four chamber view of the fetal heart

Transposition of the great arteries	Mild/moderate coarctation
Tetralogy of Fallot	Mild/moderate pulmonary and aortic stenosis
Double outlet right ventricle	Small ventricular septal defect

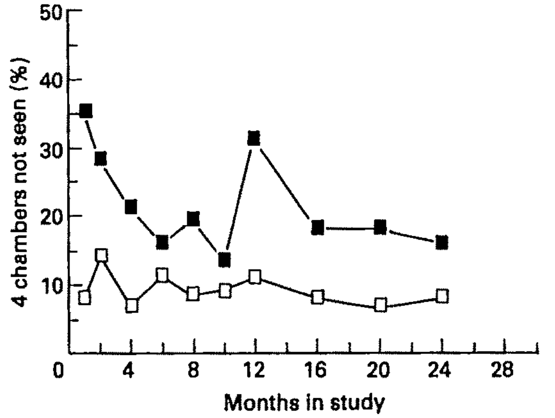


Fig. 3. Percentage of fetuses in whom the four chamber view of the fetal heart was not seen, using two different ultrasound machines. Machine 1 had both a 5 MHz and 3·5 MHz tranducer and provided images of much higher resolution than machine 2, which only had a 3·5 MHz transducer. Both types of imaging system were operated by the same staff, in the same unit. The results shown are from Unit 3, where approximately 4880 pregnant women were screened for congenital heart disease during 24 months of the study period. —□— machine 1; —■— machine 2.

is inconsistent with the conclusions of the Northern Regional abnormality survey which stated that the sensitivity of antenatal diagnosis for cardiac malformations remains poor (Members of the Joint Study Group on Fetal Abnormalities 1989). In a recent study from a referral centre for paediatric cardiology in a different region (Cullen *et al.* 1990), it was estimated that of 431 newborn infants presenting with congenital heart disease, 222 were potentially detectable by examining the four chamber view. In 81 of the 431 the study was prospective so that the prenatal history could be obtained. It was estimated that 55 of the 81 could have been detected by four chamber view screening but only five had been diagnosed prenatally. In 54 of the 81 (67%), the routine scan was performed before 18 weeks gestation. The authors concluded that mid-trimester detection of cardiac malformation was poor and that training at primary scan level, together with modification of the timing of the routine scan, was required. We think that this can be done.

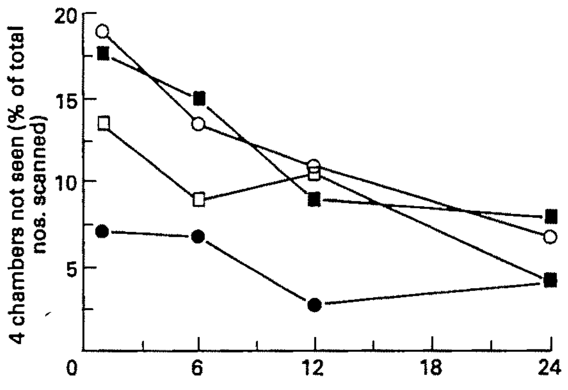


Fig. 4. The changes in the percentage of fetuses in whom the four chamber view of the fetal heart could not be adequately achieved on the first attempt, in Units 1, 2, 3 and 4 in the study. over a 2 year period. The numbers of pregnant women screened in each unit, during the 24 month period shown, were approximately 4530, 3640, 4880, and 5780 respectively. —●— Unit 1, —□— Unit 2; —○— Unit 3; —■— Unit 4.

The World Health Organisation criteria for screening are as follows: (1) The condition should be of sufficient frequency and severity; (2) The condition should cause a known spectrum of symptoms; (3) The screening test should be simple, reliable, and have a low incidence of false positive and false negative results; (4) Adequate methods of confirmation and follow-up must be available; (5) The condition should be amenable to treatment; and (6) Ideally there should be a cost advantage to society.

Screening for congenital heart disease by examination of the four chamber view on routine obstetric scans fulfils most of the above criteria. Congenital heart disease is a common congenital abnormality, the reported incidence varying betwen 4–10 per 1000 live births (Hoffman 1990). The forms of congenital heart disease detectable on four chamber examination alone will be present in 1 in 500 pregnancies and are usually at the severe end of the spectrum of cardiac malformation (Allan *et al.* 1985). Examination of the four chamber view is a simple and reliable means of screening, provided the operator has learnt to obtain and interpret the view correctly. The proportion of false positive and false negatives could still be improved in the units performing the primary screening scan, but is low in the specialist unit to which the pregnancies are referred (Allan *et al.* 1989). With increasing experience and improving technology it is very likely that this will improve in the screening units so that the number of abnormalities missed is minimal and the majority of referrals to a specialised unit are true positives.

Of the 53 abnormalities detected on screening, 45 were detected and referred at a gestation at which termination of pregnancy was an option and 36 pregnant women chose this course. The diagnosis of heart disease was confirmed at postmortem study in all except two of the fetuses following a termination or a spontaneous intrauterine death. Permission for autopsy was refused in these two fetuses. In all of the fetuses with predicted heart disease born alive, the diagnosis of heart disease was confirmed postnatally either by echocardiography, cardiac catheterization, or at operation or postmortem.

Although it is difficult to estimate the exact cost effectiveness of this type of screening programme because of the number of pregnancies terminated, there were 36 fewer babies born who would have presented to a paediatric cardiology unit or would have needed a neonatal cot. It is possible that some of these might have died *in-utero*, but the majority would probably have reached term. If screening is implemented effectively in all the obstetric units in this country and if the proportion of parents electing to end the pregnancy, when there is major disease in the fetus, stays the same as that experienced

Table 6. The outcome for 53 fetuses with congenital heart disease detected by screening

Outcome	Numbers	Percentage (%)
Termination	36	68
Intrauterine death	4	8
Neonatal death	9	17
Alive	4	8

in our unit, the number of newborn infants presenting to paediatric cardiology units will be significantly altered. An important benefit of prenatal diagnosis of congenital heart disease is to allow planning of delivery in a unit with paediatric cardiology facilities available, so that postnatal care can be optimal and the transfer of a sick baby avoided.

There are several factors that seemed to be important in influencing the results obtained in the units selected for study. The enthusiasm and attitude of the staff were often reflected in the results. There were two units that were initially reluctant to join in the study. The inclusion of the four chamber view was initially thought to be time consuming and the ultrasonographers were reluctant to recall pregnant women in whom the four chamber view had not been seen, as they thought this would take up too much scan time. However, the realization that congenital heart disease is more common than many of the other types of structural anomalies sought for on a routine scan, and that severe forms can be fatal, helped to change such an attitude, particularly after a major cardiac abnormality had been missed. Thus, with increasing enthusiasm as the study progressed, ultrasonographers became more familiar with the normal features of the four chamber view, found it easier to incorporate it into the routine scan, and came to regard examination of the four chambers of the heart as an essential part of the scan. As a result, the percentage of fetuses in whom four chambers were seen at the first attempt improved and the number recalled when the four chambers had not been seen also increased, so that there was only a small percentage in whom the four chambers were not seen finally.

The number of staff involved in scanning in each unit varied and often there were new junior staff rotating into the department. Some of the new staff were not familiar with the correct interpretation of the four chamber view and a few abnormalities were overlooked for this reason. It was, therefore, important to keep in close contact with the units on a regular basis and continue with teaching, particularly for any new recruits.

The most commonly reported reasons for not obtaining a four chamber view of the fetal heart were maternal obesity, awkward fetal lie particularly with the spine anterior, poor resolution equipment and a gestational age of less than 18 weeks. The gestational age at which the routine scans are performed is an important factor in the detection of most structural anomalies, the ideal time for examining the fetal heart being between 18–20 weeks gestation. At the start of the study, 4 of the 10 units were performing routine scans before 18 weeks which meant that there were a significant number of fetuses in whom the four chamber view could not be seen. Recalling a large number of pregnant women was not practical in terms of scanning time. However, during the course of the study, and partly as a result of it, all the units now scan at 18 weeks or later and nearly all those seen before this time are recalled.

Success in obtaining a satisfactory view of the heart was greatly influenced by the equipment being used. This varied widely from unit to unit both in quality, numbers of machines and types of transducer available for use. Since the start of the study, three units have acquired new equipment. Again, this has occurred as a result of the screening programme, as ultrasonographers have become more aware of what is missed with poor resolution equipment. Unfortunately, however, there are still units that are working with equipment which does not allow staff to detect all the malformations of which they are potentially capable.

There are many factors that will affect the efficacy of four chamber view screening but these can be changed with time and effort. Screening for congenital heart disease is already taking place in many centres in the United Kingdom. Increasing experience of ultrasonographers performing routine scans at 18–20 weeks gestation using high resolution equipment will improve the results significantly. This would have a major impact on the numbers and types of malformations presenting to paediatric cardiology units in the future.

Acknowledgments

The authors are supported by the British Heart Foundation and G.K.S. partly by the SETRHA.

References

Allan L. D , Chita S. K., Sharland G. K., Fagg N. L , Anderson R. H & Crawford D. C. (1989) The accuracy of fetal echocardiography in the diagnosis of congenital heart disease. *Int J Cardiol* **25,** 279-288.

Allan L. D., Crawford D. C , Anderson R H. & Tynan M. J (1984) Echocardiographic and anatomical correlations in fetal congenital heart disease *Br Heart J* **52,** 542-548

Allan L. D., Crawford D. C., Anderson R. H & Tynan M. J. (1985) Spectrum of congenital heart disease detected echocardigraphically in prenatal life. *Br Heart J* **54,** 523-536.

Allan L. D , Crawford D. C., Chita S. K. & Tynan M. J. (1986) Prenatal screening for congenital heart disease *Br Med J* **292,** 1717-1719

Cullen S , Franklin R., Sharland G , Allan L. & Sullivan I (1990) Potential impact of population screening for prenatal diagnosis of congenital heart disease (Abstr.) Proceedings of British Cardiac Society *Br Heart J* **64**(1), 90

Fermont L , De Geeter B., Aubry M. C., Kachener J & Sidi D. (1985) A close collaboration between obstetricians and cardiologists allows antenatal detection of severe cardiac malformations by 2D echocardiography. (Abstr) Proceedings 2nd World Congress of Paediatric Cardiology. New York, p. 10

Forfar J. O (1984) Demography, vital statistics and the pattern of disease in childhood. In *Textbook of Paediatrics* (Forfar J. O. & Arneil G. C., eds), Churchill Livingstone, p. 11.

Hoffman J I E. (1990) Congenital heart disease· Incidence and inheritance. *Pediat Clin North Am* 37(1), 25-43.

Kleinman C. S., Hobbins J. C., Lynch D. C. & Talner N. S. (1980) Echocardiographic studies of the human fetus: prenatal diagnosis of congenital heart disease and cardiac dysrhythmias. *Pediatrics* **65,** 1059-1068.

Members of the Joint Study Group on Fetal Abnormalities (1989) Recognition and management of fetal abnormalities. *Arch Dis Child* **64,** 971-976

OPCS (1986) Mortality Statistics, Perinatal and infant. social and biological factors. Series DH3, no. **20,** pp 28, 42, 48.

OPCS (1988) Congenital malformation statistics: notifications. Series MB3, no. **4,** ix

Saari-Kemppainen A., Karjalainen O., Ylostalo P. & Heinonen O P (1990) Ultrasound screening and perinatal mortality: controlled trial of systemic one-stage screening in pregnancy. *Lancet* **336,** 389-391

Sharland G. & Allan L (1990) Detection of congenital abnormalities of the cardiovascular system by ultrasound In *Modern Antenatal Care of the Fetus* (Chamberlain G., ed.) Blackwell Scientific Publications, Oxford, p 356.

Received 23 May 1991
Accepted 20 September 1991

British Journal of Obstetrics and Gynaecology
March 1992, Vol. 99, pp. 226–231

GYNAECOLOGY

The multidisciplinary management of a family with epithelial ovarian cancer

D. J. CRUICKSHANK
Senior Registrar in Obstetrics and Gynaecology
Aberdeen Royal Infirmary, Aberdeen
N. HAITES
Senior Lecturer in Clinical Genetics
S. ANDERSON
General Practitioner
H. MATHESON
Family Member
The above four authors are members of the Grampian Familial Epithelial Ovarian Cancer Study Group
c/o Medical Genetics
University of Aberdeen
Foresterhill, Aberdeen
M. H. HALL
Consultant in Obstetrics and Gynaecology
Wards 7/8, Aberdeen Royal Infirmary
B. MILNER
Research Assistant
Department of Medical Genetics
University of Aberdeen
Foresterhill, Aberdeen
A. AH-SEE
Senior Lecturer in Surgery
Department of Surgery
University of Aberdeen
I. GUNN
Consultant Surgeon
Dr Gray's Hospital, Elgin
O. EREMIN
Professor of Surgery
Department of Surgery
University of Aberdeen
F. GILBERT
Director of Breast Cancer Screening Unit
A. W. JOHNSTON
Consultant Physician
Ward 3/4
Aberdeen Royal Infirmary, Aberdeen

Correspondence: Dr D. J. Cruickshank, MRCOG, Department of Obstetrics and Gynaecology, Aberdeen Royal Infirmary, Aberdeen AB9 2ZB.

ABSTRACT

Objective To describe the management of a family with an inherited predisposition to ovarian and breast cancer. Particular attention is paid to the problems of contraception, screening, prophylactic surgery and hormone replacement therapy.

Setting The multidisciplinary Grampian Familial Epithelial Overian Cancer Study Group.

Subjects 162 members of a family extending over five generations. In the third generation, five of the 10 women died with epithelial ovarian cancer. Three women in generation IV have developed pre-menopausal breast cancer. There are now 78 family members in the fifth generation aged between 2 and 22 years.

Interventions Counselling of female family members is started at the age of 18 years. The combined oral contraceptive pill is advocated to suppress ovulation. Gynaecological follow-up after the age of 28 includes yearly pelvic examination, transvaginal ultrasonography and serum CA125 estimation. Laparoscopy with peritoneal cytology is indicated if any part of this yearly assessment is abnormal. Prophylactic oophorectomy is advised between the ages of 35 and 40 years after the family is complete. In generation IV, 20 of the 29 women have undergone prophylactic oophorectomy. Oestrogen hormone replacement therapy with a cyclical progestogen is recommended after prophylactic oophorectomy. Breast cancer screening starts at the age of 25 and involves annual clinical breast examination augmented by mammography and breast ultrasound.

Conclusions Only by the careful questioning and recording of family history, including at least third degree relatives (cousins), will similar groups with familial ovarian/breast cancer be identified. When predisposing genes are characterized it will be possible to identify carriers within the family and concentrate clinical effort on them while offering appropriate reassurance to those with decreased risk.

Epithelial ovarian cancer is the most common malignancy of the female genital tract and in contrast to the other gynaecological malignancies the incidence and mortality rate for ovarian cancer is rising (Beral *et al.* 1987). It accounts for more deaths annually than cancer of the uterine cervix and corpus together. The natural history is poorly understood, although it tends to be confined to the abdominal cavity spreading locally in the pelvis and diffusely over the peritoneal surfaces. As a result the disease is asymptomatic and undetectable in the early stages. Indeed, 70% of patients have metastases beyond the pelvis (Stage III and IV) at presentation (Piver 1983). This also explains the poor prognosis with an overall 5-year survival of approximately 25% which has changed little over the last 20 years.

It has been estimated that between and 5 and 10% of epithelial overian carcinomas are hereditary with an autosomal dominant mode of genetic transmission (Lynch *et al.* 1982; Ponder *et al.* 1990). Ponder has suggested that there are about 2000 women at high risk in the UK population aged between 25 to 40. From this group he estimates that about 500 deaths will occur from ovarian cancer by the age of 60. Piver now has

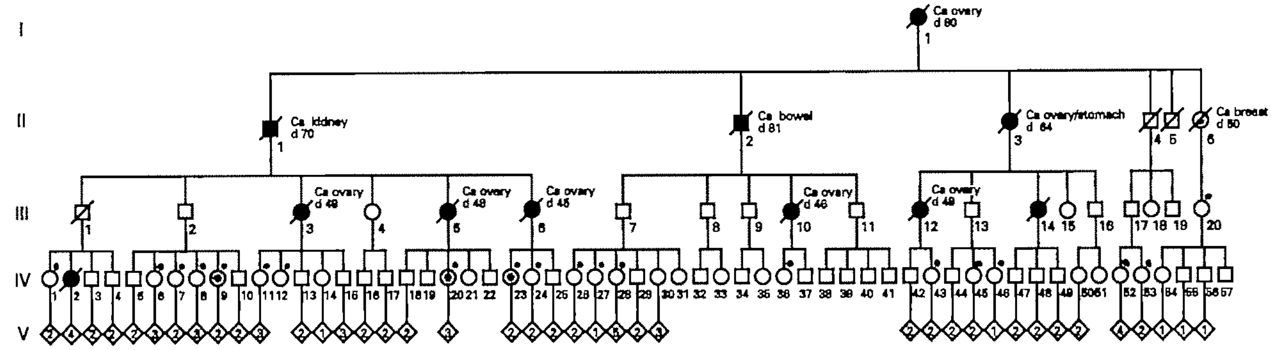


Fig. 1. A portion of the family pedigree as ascertained in 1990 showing the occurrence of an additional ovarian cancer in individual IV2 (died age 43) and premenopausal breast cancer in three other women in generation IV (nos. 9, 20 and 23) ●20 of the 29 females in generation IV are known to have had prophylactic pelvic clearance ☐ males, ○ females; there are 54 males and 33 females in generation V. Daughter of IV-25 has cancer.

176 families with familial ovarian cancer in his registry (Kullander 1990).

In this paper we describe the management of a very large and thoroughly investigated family with an inherited predisposition to ovarian/breast cancer, and discuss the problems of contraception, screening, prophylactic surgery and replacement therapy and the implications for management of similar families.

The Grampian family with hereditary epithelial ovarian cancer

The background to the discovery of this family was originally reported in 1981 (Matheson *et al.* 1981). It is particularly noteworthy that it was the family themselves who originally thought of the possibility of a family predisposition to ovarian cancer. It was in the third generation that the extent of the problem was realised by two medical members of the family after intensive research within the family. This was despite the fact that the five affected members in the third generation, as seen on pedigree (Fig. 1), all presented to the same hospital within a period of 8 years. Indeed, two of them were patients of the same general practice and died in the same year. Women, however, change their surname on marriage and the maiden name is not generally recorded in general practice records or hospital in-patient records.

Table 1. Age and survival of affected family members

Pedigree	Age at diagnosis (years)	Survival time (months)
Ovarian		
I/1	NK	Died aged 60 years
II/3	66	6
III/3	45	24
III/5	47	12
III/6	44	12
III/10	44	24
III/12	49	6
IV/2	41	17
Breast		
II/6	NK	Died aged 50 years
IV/9	35	28 months treatment*
†IV/20	30	15 months treatment*
IV/23	38	36

*Alive

†Two primary lesions.

NK = not known

Since the original publication, the family tree has grown considerably, and this highlights one of the major problems in the management of this family at present and in the future in terms of administration, education, communication and follow-up.

The pedigree (Fig. 1) shows a pattern of cancer within the family consistent with the passage of an autosomal gene which predisposes women to ovarian or breast cancer but which can be transmitted through unaffected males. As has been hypothesized by Knudsen (1971) and shown in other cancers including retinoblastoma, the full expression of the predisposing gene may be dependent on the occurrence of a somatic mutation in the normal allele resulting for homozygosity of loss of normal function in the two alleles.

In such studies one must also be aware that some cancers in individuals in the family may represent sporadic occurrences.

In generation III, five of the 10 females died with ovarian cancer between the ages of 45 and 49 years. In generation IV there are 29 women of whom 20 have had a prophylactic oophorectomy after they had completed childbearing. In most cases hysterectomy was also performed to avoid possible problems with endometrial hyperplasia associated with hormonal replacement therapy One family member declined prophylactic oophorectomy and presented at the age of 42 with FIGO Stage III disease (grade 3 serous epithelial ovarian cancer) 9 months after an apparently negative laparoscopy that included peritoneal cytology. The remaining 11 women are aged between 21 and 35 years. Table I shows that age at diagnosis, survival time and histology, where known, of ovarian and breast tumours presenting in this family. In the fifth generation there are now 78 individuals aged between 2 and 22 years. Although the majority of the family remain in the North-East of Scotland there are 12 family members with follow-up planned or taking place outwith the Grampian Region.

Management

Communication and education

Originally the task of identifying and contacting the family members at risk was undertaken manually by the authors of the original report (H.M., and S.A.). Initially where possible they visited the women in generation III and IV. Where this was not practical they talked at length with the female family members by telephone. It was necessary in most cases to repeat the information on more than one occasion. Initially the surviving women in the fourth generation were reluctant to seek medical advice despite being made aware of the family history and the risk of developing ovarian cancer. This denial was further fuelled by the practice of prophylactic pelvic clearance which distanced the reality of ovarian cancer risk until this was highlighted again when individual IV2 presented with advanced ovarian cancer in 1986.

The dissemination of the information in this fashion on the subject of ovarian cancer among family members was time consuming. It was important to take time to establish the trust and confidence of key members in each branch of the family while an awareness of the cultural mores of the extended family dictated the pace and strategies employed. It took years for some members to work through and come to terms with the implications of this inherited disorder which required the continued support and availability of two of the authors (S.A. and H.M.).

The need for computerization is evident as the family tree grows and number of women at risk mushrooms. A database has been developed in Medical Genetics which updates information on changes in surname, address and general practitioner. It is also used to initiate follow-up. A standard letter is now sent to each woman at risk before their first visit, with a copy to their general practitioner. This standard letter provides information on the family history and the inherited risk of cancer. It also emphasizes the effect of transmission through male members in the family. At this point formal genetic counselling is also made available.

Gynaecological counselling

Gynaecological referral for each female family member is initiated at the age of 18 in order to discuss the risks, the planned screening, and contraception. Incessant ovulation is one of the principal theories for the aetiology of ovarian cancer (Fathalla, 1971; La Vecchia *et al.* 1983). Ovulation inhibition with the combined oral contraceptive pill is associated with a 40% lower risk of ovarian cancer (Newhouse *et al.* 1977; Booth, 1986). Although the effect of ovulation suppression of women with familial ovarian cancer is unknown the combined oral contraceptive pill is advocated for female family members in view of the potential theoretical benefit. The principal means of ovarian cancer prevention in the family is to advise prophylactic bilateral salpingo-oophorectomy, usually accompanied by total abdominal hysterectomy. Tobacman *et al.* (1982), however, has reported intra-abdominal carcinomatosis histologically compatible with metastatic ovarian carcinoma in three of 28 women who had undergone prophylactic oophorectomy because of epithelial ovarian cancer. This may occur as a result of a field change in the coelomic epithelium elsewhere in the abdomen. Alternatively residual ovarian tissue may have been left at the time of surgery. At present prophylactic oophorectomy is advised for all women in the family as detection of the predisposing gene is not yet possible in individual cases. Prophylactic surgery is undertaken after the family is complete and as the youngest affected family member was 42 years it is suggested that this be undertaken between 35 and 40 years.

Screening for epithelial ovarian cancer in the general population is a contentious issue (Sharp 1990). As far as we are aware there is no premalignant phase. The natural history of the disease is unknown and as yet there is no satisfactory test. Ultrasound scanning and in particular transvaginal ultrasound and the tumour-associated antigen CA 125 have been advocated for the early detection of ovarian cancer (Browne *et al* 1989; Jacobs *et al* 1988). The present protocol for the follow-up of family members at risk between the ages of 28 and 30 and prophylactic oophorectomy involves yearly assessment with a pelvic examination, transvaginal ultrasound and serum CA 125 estimation. Laparoscopy, with peritoneal cytology, is indicated if any part of this yearly assessment is abnormal. Lynch *et al.* (1990) have reported on two patients among 67 high risk members from three ovarian cancer-prone families where ovarian cancer was diagnosed after presentation with elevated CA 125 levels (Lynch *et al.* 1990).

The policy regarding hormone replacement therapy after prophylactic pelvic clearance was to advise a continuous oestrogen alone. Because of the risk of breast cancer in the family this policy has been modified to include a cyclical progestogen which may have a protective effect (Grambrell, 1987).

Breast cancer risk

Over the last 2 years three women in generation IV have developed breast carcinoma. These women were aged 38, 35 and the youngest who was 30 had two separate primary carcinomas in the right breast (Table I). The first of the family members with breast cancer was on unopposed oestrogen replacement therapy at the time of diagnosis and since then the policy has been to use in addition a cyclical progestogen. One of these three women has recently died as the result of pulmonary metastases and the most recent case was only diagnosed 3 months ago. A further case of breast cancer had occurred in generation II. Breast cancer, however, is five times more common than ovarian cancer in the general population and it is possible therefore that the four cases of breast cancer in the family are sporadic. There is, however, an associated increased risk of breast cancer in women with non-familial ovarian cancer and in the context of familial cancer the breast/ovarian cancer syndrome is well recognised with an autosomal dominant pattern of genetic transmission (Lynch *et al.* 1978; Go *et al.* 1983; Prior & Waterhouse 1981). Breast cancer screening has recently been recommended as an integral part of the management of this family. An algorithm (Fig. 2) for optimal breast screening in this family was drawn up in consultation with a surgeon and radiologist from the Breast Cancer Screening Unit. A letter explaining the advisability of initiating breast screening is sent to each patient's general practitioner along with a copy of the algorithm. Optimally screening would be performed by the Breast Cancer Screening Unit but the current guidelines do not allow this and it is suggested that general practitioners direct their patients via their local surgical breast clinic. A letter explaining the need for screening is also sent out to the female family members at the age of 25 or over and screening takes the form of annual clinical examination of the

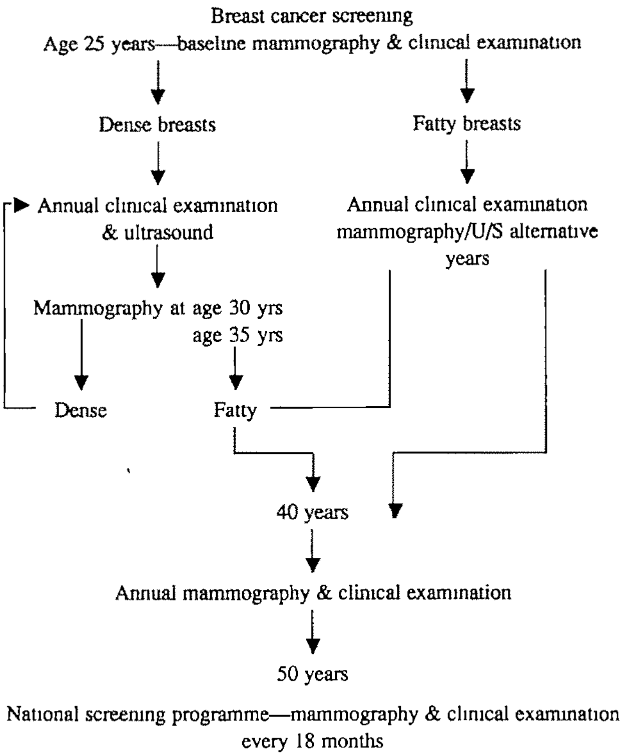

Breast cancer screening
Age 25 years—baseline mammography & clinical examination
Dense breasts
Fatty breasts
Annual clinical examination & ultrasound
Annual clinical examination mammography/U/S alternative years
Mammography at age 30 yrs
age 35 yrs
Dense
Fatty
40 years
Annual mammography & clinical examination
50 years
National screening programme—mammography & clinical examination every 18 months

Fig. 2. A flow chart indicating breast cancer screening for women in the family

breasts augmented by mammography and breast ultrasound according to the characteristics of the breast tissue. With this protocol it is considered that the risk of x-ray induced carcinoma is less than the risk of familial breast cancer. Screening for breast cancer, however, in premenopausal women is of debatable value. As with ovarian cancer these tests are designed to detect carcinoma at an early stage rather than a premalignant process. It follows that prophylactic bilateral mastectomy may be considered appropriate by some women at high risk. This is an area which as yet has not been fully explored. Fear of breast cancer may evoke strong emotions among women whereas bilateral mastectomy in the absence of breast carcinoma would be expected to be associated with significant psychosexual morbidity. Given the potential for multifocal breast cancer development as occurred in the most recently diagnosed family member, it has been suggested that conservative breast surgery may not be appropriate as the theoretical risk of malignant transformation in the residual breast tissue with a genotype predisposing to breast cancer.

Discussion

Given the present limitations in attributing risk within this family based currently on pedigree analysis alone, the problems of co-ordination, communication, follow-up and management will increase as the family expands. A centralized computer-based registration is essential. Until such times as a genetic marker is found to predict risk more accurately in individual family members our screening and prophylactic measures will remain crude and cumbersome. The women will have to continue to experience anxiety associated with screening, major surgery in the form of prophylactic pelvic clearance and, in some cases, prophylactic mastectomy. If prophylactic surgery does prevent clinical disease it will become impossible to detect gene carriers and, hence, as the empirical risk of being a gene carrier halves in succeeding generations, screening and surgery will become apparently less justifiable.

Over the last few years our understanding of some of the molecular events involved in the development of breast and, more recently, ovarian cancer has greatly increased. Ponder *et al.* (1990) reporting on an OPCS study (data from the Office of Population and Censuses and Surveys) commented that the lifetime risk to a sister or mother of a patient in a family where two or more close relatives are affected with ovarian cancer is about 40%. On the genetic hypothesis, this is explained as a 50% chance of inheriting the gene and an 80% chance that a gene carrier will develop ovarian cancer. Recently linkage was established, in five families with early-onset breast cancer, to a locus on chromosome 17q (Hall *et al* 1990). In addition it has been shown that in some families with Li Fraumeni syndrome (soft-tissue sarcomas, breast and other cancers) the mutation causing the predisposition is in the p53 gene on chromosome 17p (Srivastava *et al* 1990). Loss of heterozygosity in both breast and ovarian cancer has been found on chromosome 17p and q and other regions of the genome (Ehlen & Bubeau, 1990; Thompson *et al* 1990).

In the ovarian tumour from individual IV2 in Fig. 1, allele loss has been found for loci on both 17p and 17q (Milner *et al* 1990), but no evidence of somatic mutations have yet been found in any member of the family.

Linkage studies are now possible using techniques which include the polymerase-chain-reaction (PCR). This technique can be used on degraded DNA, such as is obtained from paraffin embedded tissue and will thus make available both normal and tumour DNA from deceased individuals from within the family.

It is hoped that it will soon be possible to identify the carriers of the predisposing gene in this family and to direct screening and prophylactic surgery to the individuals found to be at high risk.

It has been suggested that ovarian cancer-prone families are ideal for the assessment of screening methods for ovarian cancer. In fact, this is not logical as prophylaxis in the form of oophorectomy is preferred by the women concerned to continued screening with the hope of detecting cancer development at an early stage. There still remains, however, the risk of familial peritoneal ovarian carcinomatosis syndrome after prophylactic oophorectomy (Tobacman *et al* 1982; Chen *et al.* 1985). Hereditary ovarian cancer-prone families illustrate a cost-effective model for cancer prevention and control. Despite Liber's call for a detailed family history and development of a modified nuclear pedigree on all patients presenting with ovarian cancer in order to identify families at risk, there is little evidence that this has been taken seriously. It is obviously an important issue as it is a simple inexpensive approach to cancer prevention (Liber 1950) and would only require a detailed family pedigree which at the very least, includes cousins.

One area which does not seem to have been addressed at any great length in previous publications on familial ovarian/breast cancer is the potential benefits and risk associated with the combined oral contraceptive pill and hormone replacement therapy. The recent development of breast cancer in this family has made this particular issue more prominent. Oophorectomy has a protective effect on the occurrence of breast cancer and it has been suggested that earlier prophylactic oophorectomy would be considered. If malignant transformation in the breast occurs some 10 or more years before clinically apparent disease, the potential beneficial effect of earlier prophylactic oophorectomy is likely to be small. The youngest women with breast cancer in this family was diagnosed at the age of 31. As mentioned earlier, there is little doubt that oral contraceptive use protects against ovarian cancer (Cancer & Steroid Hormone Study Group 1987). The relation between the pill and breast cancer, however, is less clear. At present there is no convincing evidence for a cause and effect association (Vessey *et al.* 1989) and any relation with an increased risk of breast cancer in pill users is likely to be very complex. Current opinion seems to suggest that it is the larger dose preparations used from a young age and on a long term basis which promote earlier clinical manifestation of breast cancer in some women while having no net impact on their lifetime risk of the disease (Schlesselsman 1989; McPherson *et al.* 1987).

With regard to oestrogen hormone replacement therapy and its effect on the risk of ovarian cancer, there is no clear evidence of a strong association and conflicting reports have been published (Weiss *et al.* 1982; Franchesci 1982). Extrapolation from the known protective effect of the combined pill on ovarian cancer has led to the suggestion that cyclical oestrogen-progestogen HRT might also lead to a protective effect with regard to ovarian cancer.

Hormone replacement therapy in the form of a cyclical oestrogen-progestogen preparation is used in this family after prophylactic oophorectomy. The concern, therefore, is the effect of these hormones on the risk of breast cancer. From a meta-analysis involving 23 separate studies it was concluded that there was no evidence to implicate oestrogen replacement therapy in the aetiology of breast cancer (Armstrong 1988). The only group where there was a suggestion of an increased relative risk of breast cancer was in women with a positive family history of breast cancer (relative risk 1·25) but this was not statistically significant (Armstrong 1988). Hunt *et al.* (1987) reported findings from a cohort study and found a lower than expected mortality from breast cancer but an increased incidence of the disease in 4544 British women receiving hormone replacement therapy with 40% on a cyclical progestogen. In a recent review including eight cohort studies, it was concluded that although ever-use of oestrogen replacement therapy is associated either with no increase or a very modest increase in breast cancer risk, there is mounting evidence for some increase (around 50%) in breast cancer with longer durations of use (Hunt & Vessey 1991). Data on the effect of progestogens in opposed HRT on breast cancer risk are lacking. Initial reports suggested a protective effect of added progestogen when compared with unopposed HRT (Grambell 1987). Three subsequent studies, however, have failed to confirm this protective effect (Hunt & Vessey 1991) although progestogens are of recognized therapeutic benefit in established breast cancer.

There is little doubt that oestrogen hormone replacement therapy is indicated after oophorectomy in young women. The benefits include symptomatic relief, protection against osteoporosis, ischaemic heart disease, hypertension and stroke. The only real contraindication to oestrogen hormone replacement therapy is oestrogen-dependent malignancy-established breast cancer. The difficulty lies therefore in the women in this family with breast cancer at an early age and menopausal because of prophylactic oophorectomy. Progestogens are not contraindicated and have the potential to protect against bone loss and control the vasomotor symptoms in some women. There is also evidence that osteoporosis protection may be achieved with diphosphonates. Neither of these, however, have any protective effect with regard to cardiovascular disease and indeed many progestogens have an adverse effect on the lipoprotein profile making this atherogenic. Adjuvant tamoxifen in breast cancer seems to be associated with the reduction in the incidence of death from cardiovascular disease from the preliminary findings of the Scottish Adjuvant Trial (Anon 1987). Tamoxifen is an anti-oestrogen but does in fact have some oestrogenic effects. It may therefore also have a protective effect with respect to osteoporosis. Tamoxifen may also reduce the incidence of second cancers occurring in the remaining breast of women after initial primary treatment for breast cancer (Cuzick & Baum 1985). From this a randomized study of tamoxifen in the prophylaxis of breast cancer in the general population has been started (Powles *et al.* 1989). Tamoxifen therefore may have a place in this family with hereditary ovarian/breast cancer as prophylaxis against the development of breast cancer. There is insufficient information, however, on the long term use of tamoxifen with regard to its benefits and risks.

Acknowledgments

Without the consistent support and co-operation of the members of the family and the general practitioners this work would not have been possible. In particular we acknowledge the tireless efforts of the late Dr J. A. B. Matheson. We are also grateful for financial support from the Grampian Health Board and the Scottish Hospitals Endowment Trust. The manuscript was typed by Miss Rebecca Moir.

References

Anon (1987) Report from the Scottish breast cancer trials. Adjuvant tamoxifen in the management of operable breast cancer. The Scottish Trial. *Lancet* **ii**, 172-175.

Armstrong B R. (1988) Oestrogen therapy after the menopause—boon or bane? *Med J Aust* **148**, 213-214.

Beral V. (1987) The epidemiology of ovarian cancer. In *Ovarian Cancer—the Way Ahead* Proceedings of the Seventeenth Study Group of the Royal College of Obstetricians and Gynaecologists in conjunction with the Helene Harris Memorial Trust. (Sharp F. & Soutter W P eds), RCOG, London, pp. 21-31.

Booth M. (1986) Aspects of the epidemiology of ovarian cancer. *PhD Thesis* London University

Browne T., Campbell S., Steer C., Whitehead M. I & Collins W. P. (1989) Transvaginal colour flow imaging: a possible new screening technique for ovarian cancer. *Br Med J* **299**, 1367-1370.

Cancer and Steroid Hormone Study Group (1987) The reduction in risk of ovarian cancer associated with oral contraceptive use *N Engl J Med* **316**, 650-655.

Chen K T., Schooley J. L. & Flam M. S. (1985) Peritoneal carcinomatosis after prophylactic oophorectomy in familial ovarian cancer syndrome *Obstet Gynecol* **66** (suppl 3), 93s-94s.

Cuzick J. & Baum M. (1985) Tamoxifen and contralateral breast cancer. *Lancet* **ii,** 282.

Ehlen T. & Bubeau L (1990) Loss of heterozygosity on chromosomal segments 3p, 6q and 11p in human ovarian carcinomas. *Oncogene* **5,** 219-223.

Fathalla M. F. (1971) Incessant ovulation: a factor in ovarian neoplasia. *Lancet* **ii,** 163.

Franchesci S., La Vecchia, C., Helmrich S P., Mangioni C. & Tognoni G. (1982) Risk factors for epithelial ovarian cancer in Italy. *Am J Epidemiol* **115,** 714-719.

Gambrell R. D (1987) Hormone replacement therapy and breast cancer *Maturitas* **9,** 123-133.

Go R. C. P., King M. C., Bailey-Wilson J., Elston R. C & Lynch H. T. (1983) Genetic epidemiology of breast cancer and associated cancers in high risk families, parts I and II. *J Natl Cancer Inst* **71,** 455-467.

Hall J. M , Leie M K , Newman B., Morrow J. F, Anderson L. R., Huey B & King M. C. (1990) Linkage of early-onset familial breast cancer to chromosome. *Science* **250,** 1684-1689.

Hunt K., Vessey M., McPherson K. & Coleman M (1987) Long term surveillance of mortality and cancer incidence in women receiving hormone replacement therapy *Br J Obstet Gynaecol* **94,** 620-634.

Hunt K & Vessey M (1991) The risks and benefits of hormone replacement therapy: an updated review. *Current Obstetrics and Gynaecology* **1,** 21-27.

Jacobs I J., Stabile I., Bridges J., Kemsley P., Reynolds C , Grudzinskas J. & Oram P. (1988) Multimodal approach to screening for ovarian cancer. *Lancet* **i,** 268-271.

Knudson A. G. (1971) Mutation and cancer statistical study of retinoblastoma. *Proc Natl Acad Sci USA* **68,** 820-824.

Kullander S. (1990) Genetic perspectives in ovarian cancer. In *Ovarian cancer, Biological and Therapeutic Challenges* (Sharp F., Mason W. P. & Leake R E., ed), Chapman & Hall Medical, London, pp 21-23

La Vecchia C., Franceschi S , Gallus G., Decarli A , Liberati A. & Tognoni G. (1983) Incessant ovulation and ovarian cancer: a critical approach. *Int J Epidemiol* **12,** pp. 161-164.

Liber A F. (1950) Ovarian cancer in mother and five daughters. *Arch Pathol* **49,** 280-290.

Lynch H. T, Albano W. A., Lynch J. F, Lynch P M. & Campbell A. (1982) Surveillance and management of patients at high genetic risk for ovarian carcinoma. *Obstet Gynecol* **59,** 589-596

Lynch H T., Conway T & Lynch J. (1990) Hereditary ovarian cancer. In *Ovarian Cancer—Biological and Therapeutic Challenges,* (Sharp F., Mason W. P. & Leake R. E., eds), Chapman & Hall Medical, London, pp. 7-19.

Lynch H. T., Harris R E., Guirgis H A., Maloney K., Carmody L & Lynch J. F. (1978) Familial association of breast/ovarian cancer. *Cancer* **41,** 1543-1548.

McPherson K., Vessey M. P., Neil A., Doll R., Jones L. & Roberts M (1987) Early oral contraceptive use and breast cancer. Results of another case-control study *Br J Cancer* **56,** 653-660.

Matheson J. A B., Matheson, H. & Anderson S. A. (1981) Familial ovarian cancer 'How rare is it'? *J R Coll Gen Pract* **31,** 743-745.

Milner B. J., Haites N E., Kelly K. F, Hall M., Kitchener H & Johnston A. (1990) Detection of allele loss in ovarian cancer. *Br J Cancer* (abstract) **62** No. 3, 546.

Newhouse M. L., Pearson R. M., Fullerton J. M., Boesan E. A. M. & Shannon H. S (1977) A case control study of carcinoma of the ovary. *Br J Prev Soc Med* **31,** 148-153.

Piver S. (1983) *Ovarian malignancies—Current Reviews in Obstetrics and Gynaeclogy* Churchill Livingstone, Edinburgh.

Ponder B. A. J., Easton D. F. & Peto J. (1990) Risk of ovarian cancer associated with a family history: Preliminary report of the OPCS study. In *Ovarian Cancer—Biological and Therapeutic Challenges,* (Sharp F., Mason W. P & Leake R E , eds), Chapman & Hall Medical, London, pp. 3-6.

Powles T J., Hardy J R., Ashley S. E. *et al* (1989) A pilot trial to evaluate the acute toxicity and feasibility of tamoxifen for prevention of breast cancer. *Br J Cancer* **60,** 126-131.

Prior P., Waterhouse J. A H. (1981) Multiple primary cancers of the breast and ovary. *Br J Cancer* **44,** 628-636.

Schlesselsman J. J (1989) Oral contraceptives in relation to cancer of the breast and reproductive tract—an epidemiological review. *Br J Family Planning* **15,** 23-33

Sharp F. (1990) Screening for early ovarian cancer. report of a workshop to the UKCCCR subcommittee for coordination of research into gynaecological cancers. In *Ovarian Cancer—Biological and Therapeutic Challenges.* (Sharp F., Mason W. P. & Leake R. E., eds), Chapman & Hall Medical, London, p. 461

Srivastava S., Zdu Z , Pirollo K., Blattener W & Chang E H. (1990) Germ-line transmission of a mutated p53 gene in a cancer-prone family with Li-Fraumeni syndrome. *Nature* **348,** 747-749.

Thompson A M., Steel C. M., Chetty V., Hawkins R. A., Miller W. R , Carter D. C., Forrest A. D. M. & Evans H. I. (1990) p53 gene mRNA expression and chromosome 17p allele loss in breast cancer *Br J Cancer* **61,** 74-78.

Tobacman J. K., Tucker M. A., Kase R , Greene M. H., Costa J. & Fraumeni J. F (1982) Intra-abdominal carcinomatosis after prophylactic oophorectomy in ovarian cancer-prone families. *Lancet* **ii,** 795-797.

Vessey M. P., McPherson K., Villard-MacKintosh L., Yeates D (1989) Oral contraceptives and breast cancer. latest findings in a large cohort study *Br J Cancer* **59,** 613-617.

Vessey M. P., Villard-MacKintosh L., McPherson K. & Yeates D. (1989) Mortality among oral contraceptive users. 20 year follow-up of women in a cohort study. *Br Med J* **299,** 1487-1491

Weiss N. S , Lyon J. L., Krishnamurthy S., Dietert S. E., Liff J. M & Daling J R. (1982) Non-contraceptive oestrogen use and the occurrence of ovarian cancer. *J Natl Cancer Inst* **68,** 95-98.

Received 21 February 1991
Accepted 25 September 1991

British Journal of Obstetrics and Gynaecology
March 1992, Vol. 99, pp. 232–238

GYNAECOLOGY

Which hormone tests for the diagnosis of polycystic ovary syndrome?

S. ROBINSON
D. A. RODIN
Endocrine Research Group
Clinical Research Centre
Watford Road
Harrow, Middlesex, UK.

A. DEACON
Department of Clinical Chemistry
Northwick Park Hospital
Harrow, Middlesex, UK

M. J. WHEELER
Department of Chemical Pathology
St Thomas's Hospital Medical School
London, UK

R. N. CLAYTON
Endocrine Research Group
Clinical Research Centre
Watford Road
Harrow, Middlesex, UK

ABSTRACT

Objective To assess the frequency of abnormal values for hormone measurements commonly used in the biochemical diagnosis of polycystic ovary syndrome (PCOS).

Design Hormone measurements in 63 unselected women with clinical and ultrasound diagnosis of PCOS attending gynaecological and general endocrine clinics in a District General Hospital were compared with those from a group of 20 normal ovulatory controls in the early follicular phase of their cycles.

Measurements Serum levels of luteinizing hormone (LH), follicle stimulating hormone (FSH), LH/FSH ratio, total testosterone, derived free testosterone, sex hormone binding globulin, androstenedione. and dehydroepiandrosterone (DHEA) were measured by radioimmunoassays. LH and FSH measured by two different assays.

Results The mean serum LH and LH/FSH ratio were significantly ($P<0{\cdot}01$) higher in the women with PCOS compared with the normal group, but these two measurements were in the abnormal range for only 35% and 41–44%, respectively. Absolute gonadotrophin values were significantly different using the two assay methods, which employed the same reference preparation as standard. Mean serum total testosterone concentration was significantly higher in the PCOS group and was the most frequently (70%) abnormal biochemical marker for PCOS. Sex hormone binding globulin (SHBG) did not differ significantly between the two groups but showed a negative correlation with body mass index in women with PCOS. The combination of SHBG and testosterone to derive a free testosterone value did not further aid the biochemical diagnosis of PCOS. Androstenedione was significantly higher in the PCOS group than in the control group, with a frequency of 53%. There was no significant difference in DHEA-S between the two groups.

Conclusion When typical ovarian ultrasound appearances plus the clinical features of oligomenorrhoea and/or hirsuitism were used to define PCOS total testosterone was the best single hormonal marker of the condition. Testosterone, androstenedione or LH, either alone or in combination, were raised in 86% of women with PCOS and these should be the definitive hormonal tests. Using LH/FSH ratio as a biochemical criterion for diagnosis of PCOS should be abandoned because of its low sensitivity. To be of value the normal range for all hormones should be precisely defined in a group of regularly ovulating women in the early follicular phase of the cycle for the assay used in each laboratory.

The original report of polycystic ovary syndrome (PCOS) by Stein & Leventhal (1935) described the clinical features of obesity, amenorrhoea, infertility and hirsutism in association with bilaterally enlarged cystic ovaries showing a typical histological appearance of thickened capsule, multiple cysts and dense hypertrophied interstitial tissue. Subsequently, it has been realized there is a spectrum of disorders associated with the same morphological ovarian appearance, ranging from the severe form in the original description, through various degrees of hirsuitism, oligomenorrhoea and obesity, to those subjects with polycystic ovaries alone, with minimal clinical features such as regular menstruation with anovulation (Conway *et al.* 1989; Franks 1989). High resolution ultrasound scanning has greatly facilitated the detection of morphologically polycystic ovaries in patients suspected of fitting the clinical syndrome since histological and morphological appearance correlates well with the ultrasound appearance (Adams *et al.* 1986; Eden 1988; Saxton *et al.* 1990). Before the widespread use of ultrasound, considerable emphasis was placed on the hormonal changes for diagnosis (Reber *et al* 1976; Yen, 1980; Lobo *et al.* 1981), although with recognition of the widening clinical spectrum, these criteria need reassessment.

For example, it has long been realized that urinary and serum luteinizing hormone (LH) concentrations are elevated in

Correspondence: Professor R. N. Clayton, Department of Endocrinology, North Staffordshire Royal Infirmary, Princes Road, Hartshill, Stoke-on-Trent ST4 7LN, UK.

PCOS (Yen *et al* 1970; Reber *et al* 1976) while serum FSH is unchanged or slightly suppressed. Because of this and the pulsatile nature of LH release, a LH/FSH ratio was devised as an important diagnostic criterion, although the proportion of subjects with a raised LH/FSH ratio seems to depend on an arbitrarily chosen value. Most workers report a LH/FSH ratio 3:1 as a diagnostic criterion for the syndrome (Lobo *et al* 1981; Shoupe *et al.* 1983; Chang *et al.* 1983), others 2·5:1 (Dunaif *et al.* 1985; Calogero *et al.* 1987), and more recently others have abandoned the ratio and relied on absolute LH values (Mavroudis *et al.* 1988; Golland *et al.* 1990) or not even considered serum gonadotrophins as diagnostic criteria (Dunaif *et al.* 1988; Conway *et al* 1989; Kiddy *et al.* 1990; Obhrai *et al.* 1990), but relied solely on clinical features with or without biochemical evidence of hyperandrogenism.

Steroid hormones of either adrenal or ovarian origin (testosterone, androstenedione and dehydroepiandrosterone (DHEA) sulphate are usually elevated in PCOS (Dunaif *et al* 1988) and sex hormone binding globulin (SHGB) is often reduced (Franks 1989), especially in obese subjects with the syndrome (Plymate *et al.* 1981; Kiddy *et al.* 1990). There is continued debate over which gland, adrenal or ovary, is the major source of excessive androgens, although recent findings of normal serum levels of 11-beta-OH androstenedione, an exclusively adrenal metabolite of androstenedione, argue against an adrenal abnormality (Franks 1989).

Thus, several different hormones have been used as diagnostic criteria for PCOS, a raised LH, an LH/FSH ratio >3 and elevated androgens. We found that women with the clinical features of PCOS did not have a high LH/FSH ratio, especially when the assay for gonadotrophins was changed from radioimmunoassay (RIA) to an immunoradiometric assay (IRMA). Consequently, we decided to assess the frequency with which serum LH, LH/FSH ratio, as measured by two different methods, and serum androgens (total testosterone, derived free testosterone and androstenedione) were elevated in women with PCOS, and thereby their diagnostic utility.

Subjects and methods

Data from 63 women with PCOS attending gynaecological and general endocrine clinics were compared with those from 20 women from amongst hospital staff or women from couples whose infertility was due to a clearly defined male factor. All women had regular ovulatory menstrual cycles. We defined PCOS by the observation of polycystic ovaries (PCO) during pelvic ultrasound scanning associated with either oligomenorrhoea (intermenstrual interval >35 days) with or without hirsutism (Ferriman & Gallwey score >7). Polycystic ovaries were defined as ovaries containing ≥10 cysts of 2–10 mm diameter arranged around the periphery or throughout the ovary accompanied by increased stroma (Adams *et al* 1986). No individual in the study group had megalocystic ovaries associated with weight loss related or hypothalamic amenorrhoea. Ovarian volume was calculated from the formula for a prolate ellipsoid (Orsini *et al.* 1985). The mean age (SD) of the PCOS group was 27 (5·0) years compared with 26 (5·0 years) in the control group. The mean body mass index (BMI) in the PCOS group, 25·9 (6·0), was significantly higher ($P<0·01$) than that in the control group, 21·2 (1·9); 49% in the PCOS group had a BMI >25, none was underweight (BMI<17); 66·6% in the PCOS group had hirsutism and 67% oligo or amenorrhoea, many exhibiting both features. The mean ovarian volume in the PCOS group was 10·1 ml (SD4·1) compared with 5·0 ml (1·4) in the control group ($P<0·01$).

The women in the control group had normal ovaries on abdominal ultrasound, had no evidence of hyperandrogenism (hirsutism or acne), had regular menstrual cycles (intermenstrual intervals between 21 and 35 days but with no more than 4 days variation from cycle to cycle) and the study cycle was ovulatory, as defined by serial ultrasound scans and/or two luteal phase progesterone values of >25 nmol/l.

All blood samples were taken on the day of the ultrasound scan, which was performed within 5 days of menstruation in the control group and, wherever possible, the same time after a spontaneous period in the PCOS group or randomly in women with severe oligomenorrhoea or amenorrhoea. In the latter, recent ovulation was excluded by progesterone measurement (<5 nmol/l). Testosterone (Wheeler & Luther 1983), androstenedione and DHEA sulphate (Treasure *et al* 1985) were measured by radioimmunoassay as described. Sex hormone binding globulin (SHBG) was measured using the Farmos kit (Farmos Diagnostics, Finland). Derived free testosterone was calculated from the total testosterone and SHBG concentrations (Nanjee & Wheeler 1985). Table 1 summarizes the inter- and intra-assay coefficients of variation. Gonadotrophins were measured by two methods, firstly an immunoradiometric (IRMA) commercial kit incorporating two high affinity monoclonal antibodies supplied by Serono Diagnostics (UK) Ltd., Woking, Surrey, UK (Method A) and secondly a radioimmunoassay (RIA) using reagents supplied by the Chelsea Hospital for Women, London, UK (Method B). The references preparation (LH = IRP 68/40, FSH = IRP 78/549) were identical for both assay methods.

Geometric means were calculated for variables that did not have a normal distribution. Student's *t* test was used for comparison of the population means, after logarithmic transformation of the data where appropriate. Paired Student's *t* test was used for comparison of the two gonadotrophin assays. Significance was assumed if $P<0·05$. The frequency or sensitivity of measurement is defined by the proportion of samples found above the 95% confidence limit for control values.

Results

The results are summarized in Table 2.

Table 1. Coefficients of variation (CV) of the assays*

Hormone	Within assay CV (%)	Between assay CV (%)
Testosterone	3	7·1
Androstenedione	7·5	12·3
DHEAS (IRMA)	6	9
SHBG (Farmos)	3·5	6
LH (A) IRMA (Serono)	3·4	4·8
LH (B) RIA (Chelsea)	5·5	14·5
FSH (A) IRMA (Serono)	5·9	12·2
FSH (B) RIA (Chelsea)	11·8	21·7

*The CV quoted is for a hormone value close to the mean of that measured in the control group shown in Table 2.

Table 2. Geometric mean and 95% confidence limits for hormones in women with polycystic ovarian syndrome (PCOS) and women with normal menstrual cycles (control)

	PCOS (n = 63)		Control (n = 20)		P
IRMA (method A)					
LH (U/l)*	4·3	(1·0–18·8)	2·7	(1·2–6·3)	<0·01
FSH (U/l)	5·6	(1·4–9·7)	6·2	(2·7–9·7)	NS
LH/FSH*	0·85	(0·2–4·0)	0·45	(0·2–1·0)	<0·001
RIA (method B)					
LH (U/l)*	6·6	(1·9–22·8)	4·1	(2·0–8·2)	<0·005
FSH (U/l)	4·4	(1·0–7·8)	4·3	(1·3–7·3)	NS
LH/FSH*	1·6	(0·4–6·3)	1·0	(0·5–2·0)	<0·005
Total testosterone* (nmol/l)	3·0	(1·4–6·2)	1·6	(1·1–2·5)	<0·001
SHBG (pmol/l)*	30	(6–166)	44	(14–131)	NS
Derived free testosterone* (pmol/l)	64	(8–492)	37	(21·68)	<0·025
Δ4 androstenedione* (nmol/l)	9·2	(4–20)	6·0	(3·5–9·8)	<0·001
DHEAS (μmol/l)*	6·1	(2·0–11·1)	5·2	(1·6–17·5)	NS

* = data log transformed before statistical analysis.
P = significance of difference PCOS *vs* control groups.

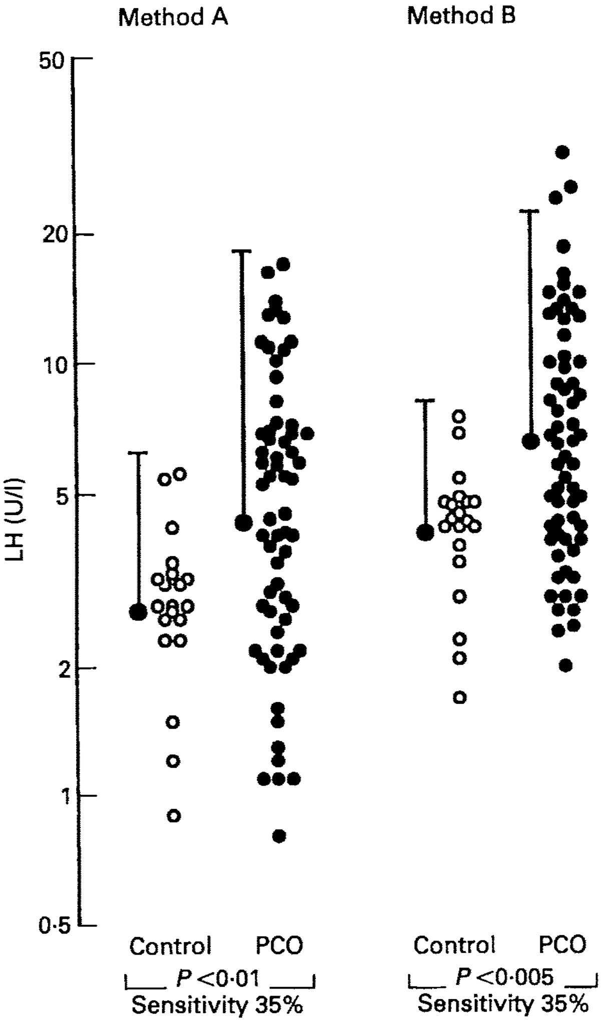


Fig. 1. Serum LH levels estimated by method A (IRMA, Serono) and method B (RIA, Chelsea) in 20 women with normal mentsrual cycles (controls) and 63 women with polycystic ovary syndrome (PCOS) Geometric mean and upper 95% confidence interval are shown Note log scale.

Gonadotrophins

The geometric mean of LH measured by the IRMA assay A and the RIA assay B was significantly higher in the PCOS group than in the control group (Fig. 1) The proportion of LH values above the upper 95% confidence interval for controls was 35% with either assay. The IRMA assay (A) gave significantly lower absolute values than the RIA assay (B) (P<0·001). In the PCOS group, using assay A the mean LH was higher (6·2 IU/l) in the 42 women with oligomenorrhoea or amenorrhoea than in the other 21 women with cycle lengths <35 days (4·2 IU/l) (P<0·05).

The mean FSH concentration in the PCOS group was not significantly different from the mean in the control group using either assay (Table 2). FSH was significantly higher measured by assay A compared with assay B (P<0·001).

The geometric mean of the LH/FSH ratios in the control group was lower than the mean in the PCOS group using either assay method (Fig. 2). The upper 95% confidence limit of the normal range was 1·0 with assay A (IRMA) and 2·0 with assay B (RIA). The frequency of high LH/FSH ratios was 41% and 44% with assays A and B, respectively. Only 3% in the PCOS group had an LH/FSH ratio >3 with IRMA (A), compared with 21% with the RIA (B).

Steroids

Total testosterone was significantly higher in the PCOS group than in the control group (Fig. 3). The frequency of high values (sensitivity) was 70%. The geometric mean of free testosterone (Table 2) was significantly higher in the PCOS group (P<0·05) and its sensitivity was 62%. In the PCOS group, the 43 hirsute women had a higher mean testosterone level (3·42, SD 1·03 nmol/l) than the other 20 women who were not hirsute (2·91 SD 0·66 nmol/l) (P<0·05). There was no correlation between mean ovarian volume and serum testosterone.

Androstenedione was significantly higher in the PCOS group than in the control group, with a sensitivity of 53% (Fig. 4). DHEAS did not differ significantly between the two groups (Table 2). SHBG did not differ significantly between the two groups but was inversely related to BMI in the two combined groups (r –0·38, P<0·001).

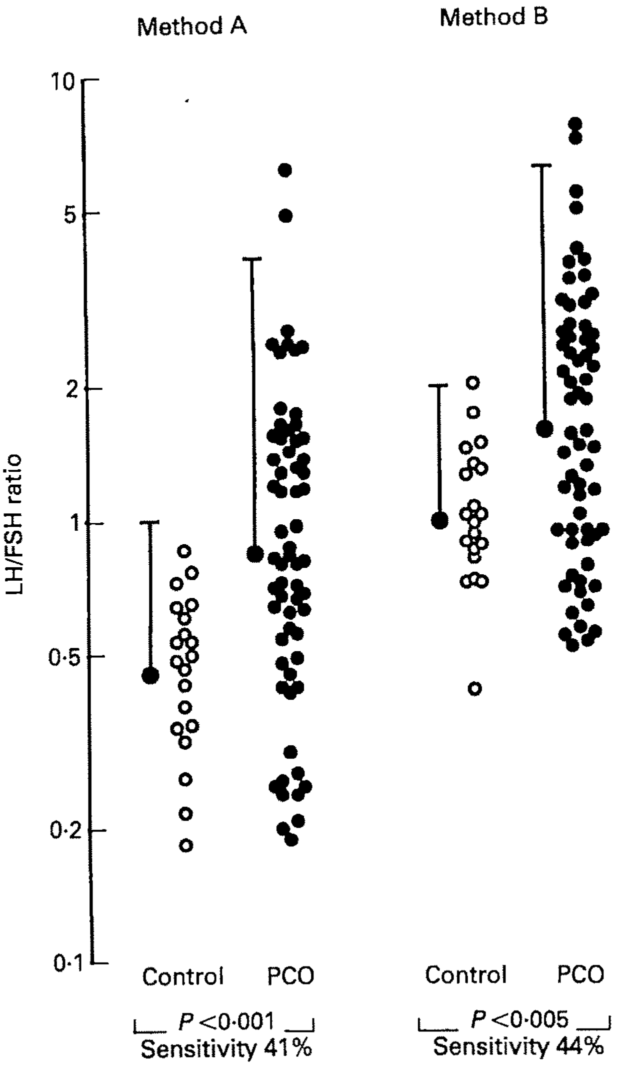


Fig. 2. LH/FSH ratio by method A and B in 20 women with normal menstrual cycles (controls) and 63 women with polycystic ovary syndrome (PCOS). Geometric mean and upper 95% confidence interval are shown Note log scale

The Venn diagram (Fig. 5) summarizes the results of the three most commonly raised hormone values. The women with a testosterone, androstenedione or LH above the 95% confidence intervals are represented by each of the three circles. Those with more than one abnormal result are represented in an overlap area. For example, in the PCOS group 21% had a raised testosterone as the only abnormal hormone result, 24% had a raised androstenedione and raised testosterone, 6% had a raised LH and testosterone, 19% had a raised testosterone, LH and androstenedione and only 3% had a raised LH or androstenedione alone. Only 14% of women with ultrasound and clinical evidence of PCOS had no abnormal levels of the hormones measured here, and 86% had one or more abnormal hormone values.

Discussion

The object of this study was to determine the frequency with which common hormone measurements were elevated in a group of women defined as having polycystic ovary syndrome on clinical grounds and whose ovaries had the typical morphological features on ultrasound. While there is debate about relying solely on ovarian ultrasound to delineate ovarian morphology because of its subjective nature, we included only those women whose scans showed unequivocally polycystic ovaries when performed by an experienced ultrasonographer and which fulfilled the strict criteria of Adams *et al.* (1986) and Eden (1988). Furthermore, other conditions that can lead to signs of hyperandrogenism and PCO were excluded (such as, Cushing's syndrome, late onset 21-hydroxylase deficiency, hyperprolactinaemia and adrenal or ovarian tumours).

The increased ovarian volume in the PCOS group agrees with prevous studies (Conway *et al.* 1989; Franks 1989) and confirms that the study population was similar in this respect to that reported by others. Although typical PCO morphological

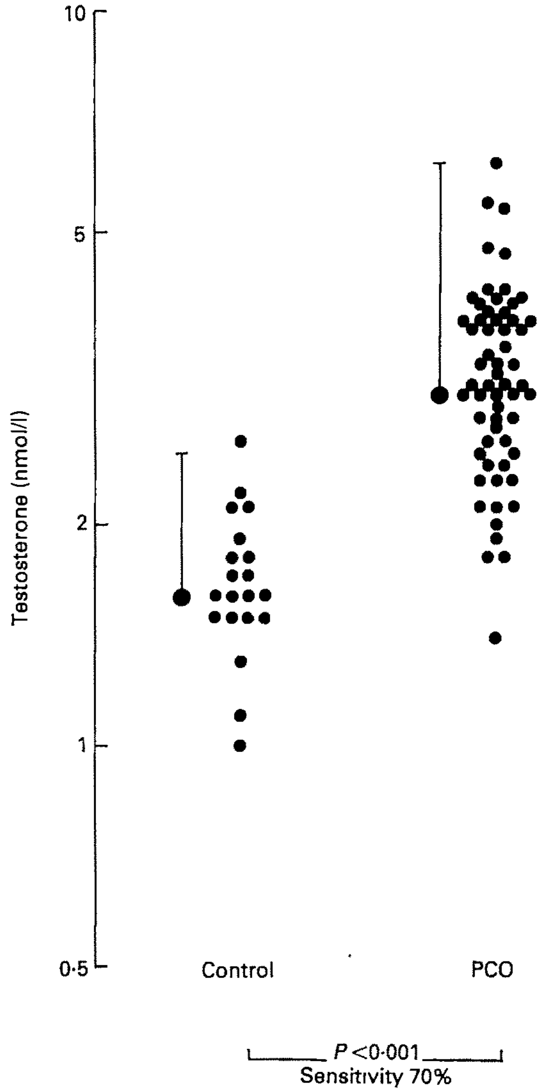


Fig. 3. Total testosterone in 20 women with normal cycles (control) and 60 women with polycystic ovary syndrome Geometric mean and upper 95% confidence interval are shown Note log scale.

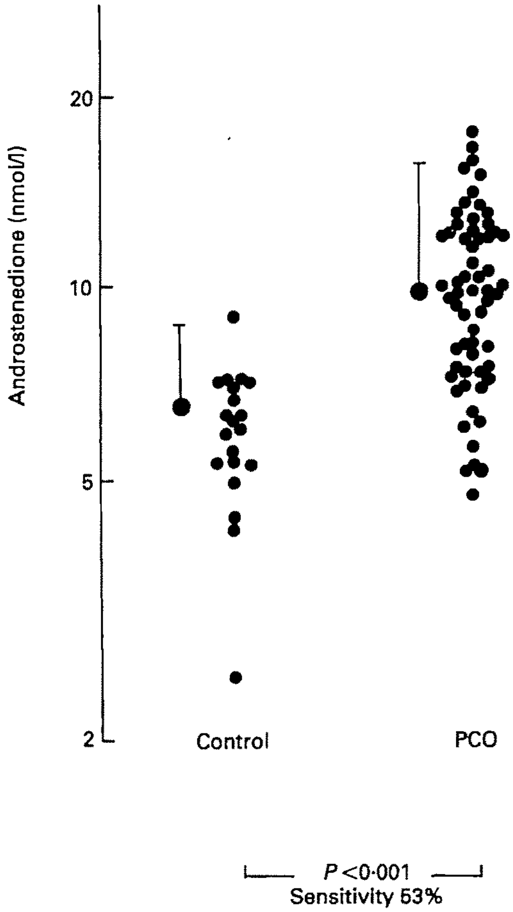


Fig. 4. Androstenedione in 20 women with normal cycles (control) and 62 women with polycystic ovary syndrome (PCOS) Geometric mean and upper 95% confidence interval are shown. Note log scale

appearances can be seen with ovaries that are of normal size this was unusual in our series. Thus, the 'gold standard' diagnostic test for PCOS in this study was the ovarian appearance on ultrasound, which was shown by Eden (1988) and Saxton *et al.* (1990) to have a specificity of 91% when compared with laparoscopic examination of the ovary. Others have not regarded this as an essential feature, rather confirming the clinical diagnosis with hormone measurements, typically the presence of hyperandrogenism and raised LH:FSH ratio (Dunaif *et al* 1985, 1988; Lobo *et al* 1983). However, what is not clear from studies in which the PCOS was defined by hormonal criteria is the proportion of women, who had the typical PCOS morphological appearances on ultrasound or, even, laparoscopically.

When considering hormonal criteria the control group used for comparison is important. In this study we rigorously confirmed ovulation in the study cycle, using serial ultrasound scans and hormone measurements throughout a complete menstrual cycle. Moreover, these women had no clinical signs of hyperandrogenism and most were of proven fertility, including three who conceived in the study cycle. In this group we have defined the upper 95% confidence limit of the hormone assays and determined the proportion of women with PCOS who had values greater than this. On this basis, testosterone and androstenedione were the most helpful hormonal markers of PCOS, with LH and the LH:FSH ratio showing much more overlap with the values in the control group (Eden 1988). However, it is clear from this, as in other recent studies (Conway *et al.* 1989; Franks 1989; Obhrai *et al.* 1990; Fox *et al.* 1991) that none of these hormones is invariably abnormal. Nevertheless, a combination of LH, testosterone and androstenedione showed an abnormality in 86% of women with PCOS making this the most useful combination. This proportion is similar to the sensitivity of 89% based on a combination of raised LH, testosterone, and free androgen index (Eden 1988; Fox *et al.* 1991).

The LH/FSH ratio was originally introduced, at least in part, to account for fluctuations in LH due to pulsatile release. A normal LH or normal LH/FSH ratio does not exclude the diagnosis of PCOS as defined clinically and by ultrasound. A high LH/FSH ratio was found to be insensitive as a diagnostic criterion with fewer than 50% of patients having an abnormal value and the previously popular use of an LH/FSH ratio >3 is not justified on the basis of our data, whichever method was used for LH measurement. Moreover, in the studies of Eden *et al.* (1988, 1989), the LH:FSH ratio was <3 in 50% of women with PCO. Further, Fox *et al.* (1991) derived a critical value for LH:FSH ratio, retrospectively, of >1, even when using RIA and polyclonal antibodies. Even with this criterion, only 67% of our PCO women had an elevated LH:FSH ratio. Our results differ from those of Obhrai *et al* (1990) who found the LH:FSH ratio to be the most common abnormal test (70%). This might reflect a subtle difference in patient population, although the clinical characteristics and ovarian morphology of the patients appeared similar. It is possible that the LH:FSH ratio might have been more sensitive if serial measurements were made. However, even though urinary LH is elevated (McArthur *et al* 1958; Yen 1970) and the amplitude of LH

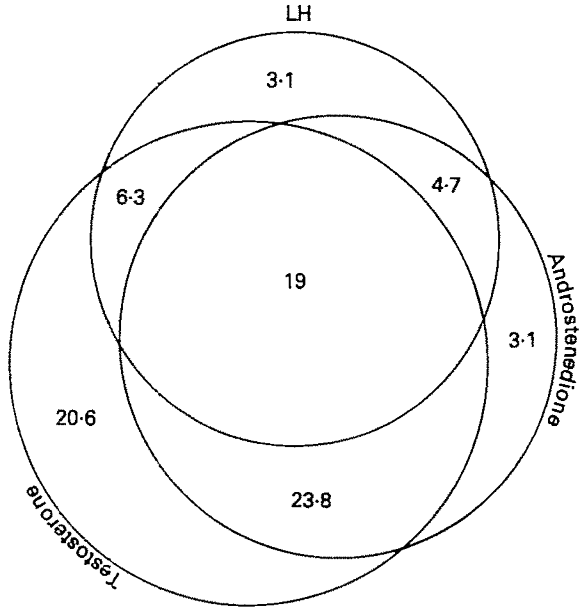


Fig. 5. Abnormal hormone values in 63 women with polycystic ovary syndrome. In this Venn diagram the three circles represent those with testosterone, androstenedione or LH above the 95% confidence limits defined by the normal ovulatory control group. Those with more than one abnormal result are represented in an overlap No abnormal hormone values in 14·2%, not every test done in 4·7%.

pulses is increased in women in PCOS (Rebar *et al* 1976; Franks 1989) it is not known what proportion of such patients display these abnormalities, suggesting that they would be equally inappropriate as diagnostic tests.

Moreover, as we have shown here, the LH:FSH ratio varies considerably according to the analytical method, especially that for LH. Ratios based on the assays reported here were considerably lower than those reported in earlier studies (Lobo *et al.* 1981; Chang *et al.* 1983; Dunaif *et al.* 1985) which used different LH and FSH reference preparations. Indeed, in a later publication, Dunaif *et al* (1988) found LH:FSH ratios as low as 0·3–0·4 in women with PCOS. It has been suggested that measurement of bioactive LH and FSH may remove many of the problems inherent with the differences in immunological assays and their reference preparations (Lobo *et al* 1983; Mavroudis *et al* 1988). However, these bioassays are impractical for routine use.

Collectively the aforementioned evidence leads us to conclude, along with others (Dunaif 1988; Franks 1989; Wheeler *et al.* 1989), that the LH:FSH ratio should be abandoned as a hormonal criterion for classication of PCOS.

Evidence of hyperandrogenaemia was common in our patients, with 78% having increased levels of either testosterone or androstenedione, or both. The proportion of women with PCOS with raised testosterone (70%) or androstenedione (53%) alone were similar to those found in a similar clinical group by Adams *et al.* (1986). However, hyperandrogenaemia is not a universal finding in this syndrome since 20–30% of patients with PCOS may have no androgen excess as assessed by urine excretion of androgen metabolites (Rodin *et al.* 1988). Plasma androgen binding is important, especially as obese women with PCOS have a low SHBG (Kiddy *et al.* 1990) thus increasing free biologically available testosterone (Yen 1980). Our data on SHBG agree with those of Kiddy *et al.* (1990). However, from our data, the use of SHBG to derive a free testosterone value does not provide additional help in the biochemical diagnosis of PCOS over and above total testosterone measurement. This contrasts with other data in which combination of testosterone and SHBG to derive a free androgen index greatly increase the sensitivity compared with total testosterone alone (Eden *et al.* 1989; Fox *et al.* 1991).

It has been suggested (Eden *et al.* 1989; Obhrai *et al.* 1990) that there is a progressive increase in steroid hormone and LH abnormality with increasing menstrual disturbance in women with polycystic ovaries. However, because of small numbers in the regular anovular cycle and amenorrhoeic subgroups and the large variability within the groups of the study of Obhrai *et al.* (1990) the significance of small changes (2-fold) in mean values is doubtful. In our study there was no marked difference in total testosterone between the oligomenorrhoeic and amenorrhoeic subgroups, though the numbers were small. Moreover, Franks (1989) could demonstrate higher testosterone and androstenedione levels only in his oligomenorrhoeic subgroup and not in those with amenorrhoea.

We did not find any correlation between ovarian volume and any of the hormones studied in agreement with others (Tabbakh *et al.* 1986; Franks 1989). However, others have shown a correlation between serum testosterone (Conway *et al.* 1989) and ovarian size although the difference in ovarian volume between patients with high and normal testosterone was small.

We conclude that gonadotrophin measurements alone have poor sensitivity in the biochemical diagnosis of PCOS and to achieve validity the normal range for serum gonadotrophins should be defined for the individual assay method in the early follicular phase of proven ovulatory cycles.

Measurement of testosterone is the most sensitive single biochemical marker of PCOS though a combination of testosterone, androstenedione, and LH increased the sensitivity to 86%.

The diagnosis of the polycystic ovary syndrome should be made on clinical features in the presence of typical appearances on pelvic ultrasound examination and hormone investigation may provide confirmatory evidence for the diagnosis.

References

Adams J , Polson D W & Franks S. (1986) Prevalence of polycystic ovaries in women with anovulation and idiopathic hirsutism. *BMJ* **293,** 335–359.

Calogero D. E , Macchi M., Montanini V. *et al* (1987) Dynamics of plasma gonadotropin and sex steroid release in polycystic ovarian disease after pituitary ovarian inhibition with an analog of gonadotropin releasing hormone. *JCEM* **64,** 980–985

Chang R. J., Laufer L. R., Meldrum D. R. *et al* (1983) Steroid secretion in polycystic ovarian disease after ovarian suppression by long-acting gonadotrophin releasing hormone agonist. *JCEM* **56,** 897–903.

Conway G. S., Honour J. W. & Jacobs H. S (1989) Heterogeneity of the polycystic ovary syndrome: clinical, endocrine and ultrasound features in 556 patients *Clin Endocrinol* **30,** 459–470

Dunaif A., Longcope C , Canick J., Badger T. & Crowley W. F. (1985) The effects of the aromatase inhibitor testolactone on gonadotropin release and steroid metabolism in polycystic ovarian disease. *JCEM* **60,** 773–780.

Dunaif A., Mandeli J., Fluhr H. & Dobrjansky A. (1988) The impact of obesity and chronic hyperinsulinaemia on gonadotropin release and gonadal steroid secretion in the polycystic ovary syndrome. *JCEM* **66,** 131–139

Eden J. A. (1988) Which is the best test to detect the polycystic ovary? *Aust NZ J Obstet Gynaecol* **28,** 221–224

Eden J. A , Place J , Carter G. D., Jones J , Alaghbaad-Zaden J. & Pawson M E. (1989) The diagnosis of polycytic ovaries in subfertile women. *Br J Obstet Gynaecol* **96,** 809–815.

Fox R., Corrigan E., Thomas P. A. & Hull M.R.G. (1991) The diagnosis of polycystic ovaries in women with oligo-amenorrhoea: predictive power of endocrine tests. *Clin Endocrinol* **34,** 127–131.

Franks S. (1989) Polycystic ovary syndrome: a changing perspective *Clin Endocrinol* **31,** 87–120.

Golland I. M , Vaughan-Williams C. A , Shalet S. M , Laing I. & Elstein M. (1990) Glucagon in women with polycystic ovary syndrome (PCO); relationship to abnormalities of insulin and androgens *Clin Endocrinol* **33,** 645–651

Kiddy D. S., Sharp P. S., White D. M. *et al* (1990) Differences in clinical and endocrine features between obese and non-obese subjects with polycystic ovary syndrome. an analysis of 263 consecutive cases. *Clin Endocrinol* **32,** 213–220.

Lobo R A., Granger L., Goebelsmann U. & Mishell D. R. (1981) Elevations in unbound estradiol as a possible mechanism for inappropriate gonadotrophin secretion in women with PCO. *J Clin Endocrinol Metab* **51(1),** 156–158.

Lobo R A , Keltsky O. A. & Campeau J. D. (1983) Elevated bioactive luteinizing hormone in women with the polycystic ovary syndrome. *Fertil Steril* **39,** 674–678.

McArthur J W., Ingersoll F. M. & Worcester J. (1958) The urinary excretion of interstitial-cell and follicle-stimulating hormone activity by women with diseases of the reproductive system. *J Clin Endocrinol Metab* **18,** 1202–1208.

Mavroudis K., Evans A., Mantora H., Anderson D. C. & Robertson W. R. (1988) Bioactive LH in women with polycystic ovaries and the effect of gonadotrophin suppression. *Clin Endocrinol* **29,** 633–641.

Nanjee M. N. & Wheeler M. J. (1985) Plasma free testosterone—is an index sufficient? *Ann Clin Biochem* **22,** 387–390.

Obhrai M., Lynch S. S., Holder G., Jackson R., Tang L. & Butt W. R. (1990) Hormonal studies on women with polycystic ovaries diagnosed by ultrasound. *Clin Endocrinol* **32,** 467–474

Orsini L. F., Venturoli S., Lorusso R., Pluchinotta V., Paradisi R. & Bovicelli L. (1985) Ultrasonic findings in polycystic ovarian disease. *Fertil Steril* **43,** 709.

Plymate S. R., Fariss B. L., Bassett M. L. & Mateji L. (1981) Obesity and its role in polycestic ovary syndrome. *J Clin Endocrinol Metab* **52,** 1246–1248.

Rebar R., Judd H. L , Yen S. S. C , Rakoff J., Vandenberg G & Naftolin F. (1976) Characterization of the inappropriate gonadotrophin secretion in polycystic ovary syndrome. *J Clin Invest* **57,** 1320–1329.

Rodin D. A., Thakkar H., Taylor N. F. & Clayton R. N. (1988) Urinary steroid excretion in women with polycystic ovary syndrome, abstract 223, *J Endocrinol* **117,** suppl (April).

Saxton D. W., Farquhar C. M., Rae T., Beard R. W., Anderson M. C. & Wadsworth J. (1990) Accuracy of ultrasound measurement of female pelvic organs. *Br J Obstet Gynecol* **97,** 695–699.

Shoupe D., Kumar D. D. & Lobar R. A. (1983) Insulin resistance in polycystic ovary syndrome. *Am J Obstet Gynecol* **147,** 588–592.

Stein I. F. & Leventhal M. L. (1935) Amenorrhoea associated with bilateral polycystic ovaries. *Am J Obstet Gynecol* **29,** 181–191.

Tabbakh G. H., Lofty I., Azab I., Rahman H. A., Southern A. L. & Aleem F. A. (1986) Correlation of the ultrasonic appearance of the ovaries in polycystic ovarian disease and the clinical, hormonal and laparoscopic findings. *Am J Obstet Gynecol* **154,** 892–895.

Treasure J. L., Wheeler M. J., Safieh B. & Russell G. F. M. (1985) Anorexia nervosa and the adrenal: the effect of weight gain. *J Psychiatr Res* **19,** 221–225.

Wheeler M. J., D'Souza A. & Horn A. N. (1989) Changing times in the measurement of gonadotrophins, abstract 30 *J Endocrinol* **123,** supp.

Wheeler M. J. & Luther F. (1983) Development of testosterone radioimmunoassays for routine use. In *Immunoassays for Clinical Chemistry,* (Hunter W H. & Corrie, J. G. T., eds) Churchill Livingstone, Edinburgh, pp. 113–116.

Yen S S. C. (1980) The polycystic ovary syndrome. *Clin Endocrinol* **12,** 177–208.

Yen S. S. C., Vela P. & Rankin J. (1970) Inappropriate secretion of follicle stimulating hormone and luteinizing hormone in polycystic ovarian disease. *J Clin Endocrinol* **30,** 435–442.

Received 1 March 1991
Accepted 24 September 1991

British Journal of Obstetrics and Gynaecology
March 1992, Vol. 99, pp 239–246

FERTILITY CONTROL

Oral contraceptive use and breast cancer risk: a meta-analysis of variations with age at diagnosis, parity and total duration of oral contraceptive use

LESLEY RUSHTON
Research Fellow
DAVID R. JONES
Reader in Epidemiology

Department of Public Health Sciences
St George's Hospital Medical School
London SW17 0RE, UK

ABSTRACT

Objective To review published reports of risk of breast cancer with oral contraceptive use.

Design Meta-analysis of study results, using regression techniques to explore the inter-study heterogeneity.

Setting Twenty-seven epidemiological studies of breast cancer risk and oral contraceptive use published 1980–1989.

Main outcome measures Relative risk of breast cancer with oral contraceptive use; variations by age at diagnosis, parity, and total duration of use, and with study design characteristics.

Results The overall relative risk estimate was 1·16 (95% CI 1·07–1·25) for the <45 years group, 1·21 (95% CI 0·99–1·47) for the nulliparous subgroup, and 1·27 (95% CI 1·12–1·44) for durations of use of more than 8 years. Source of subjects, their marital status, the type of study, data collection methods, matching for geographical area, the number of adjustment factors used in the study analysis, the country of study and the calendar period in which the study ended were all important explanatory factors for inter-study variation, but a substantial proportion of inter-study variation remained unexplained.

Conclusions These meta-analyses suggest that risk of breast cancer may be raised by around 20% in younger, nulliparous and long use duration subgroups of oral contraceptive users. Risk estimates appear to be influenced by several study design factors, which should be considered carefully in designing and reviewing future studies.

A consensus of understanding of the risk of breast cancer associated with the use of oral contraceptives (OCs) has yet to be reached in reviews of studies of breast cancer risk following OC use (Clavel *et al.* 1985; Anonymous 1985; McPherson & Drife 1986; Vessey 1986). Among the issues to be resolved are the influence of age at diagnosis, parity, age at and duration of usage, and the type and dosage of OC used. For example, 20 of the 27 studies analyzed here (Paffenbarger *et al.* 1980; Royal College of General Practitioners 1981; Pike *et al.* 1981; Trapido 1981; Brown 1981; Brinton *et al* 1982; Harris *et al.* 1982; Vessey *et al.* 1982; Pike *et al.* 1983; Hennekens *et al.* 1984; Rosenberg *et al* 1984; Stadel *et al.* 1985; La Vecchia *et al.* 1986; Lipnick *et al* 1986; Meirik *et al.* 1986; Miller *et al.* 1986; Paul *et al.* 1986; Sattin *et al.* 1986; McPherson *et al.* 1987; Ravnihar *et al* 1988; Schlesselman *et al.* 1987; Royal College of General Practitioners 1988; Stadel *et al.* 1988; Miller *et al.* 1989; UK National Case-control Study Group 1989; Vessey *et al.* 1989, Jick *et al.* 1989) have investigated breast cancer risk with OC use by age at diagnosis; 12 reported a reduced and eight a raised relative risk of breast cancer diagnosed before the age of 45.

Most reviews of epidemiological studies are narrative, but quantitative reviews or meta-analyses (Greenland 1987) are becoming increasingly common, including some in areas related to the current topic (Ewertz *et al.* 1990; Bracken 1990). Meta-analyses generally yield structured and systematic reviews using explicit criteria and methods. They offer greater potential for quantification of patterns of risk estimates, and are more easily able to cope with large numbers of primary studies than are traditional reviews. Many employ pooling and related techniques more commonly applied to clinical trial reports (Altman & Elbourne 1988; Early Breast Cancer Trialists' Collaborative Group 1990). Although tests for heterogeneity of risk between studies are performed, the implicit assumption that the relative risks (or other risk measures) of interest are constant across the studies considered, apart from sampling variations, is less likely to be true of sets of observational epidemiological studies, in which there are many potential selection and other biases (Sackett 1979).

When there are many potential sources of bias, investigation is facilitated by the use of *meta-regression* techniques (Greenland 1987; Risch 1988). In this paper we apply such methods to

---

Correspondence: Professor D. R Jones, Epidemiology and Public Health, University of Leicester, Clinical Sciences Building, PO Box 65, Leicester Royal Infirmary, Leicester LE2 7LX.

the reported results of previous studies of breast cancer risk following OC use, with the objectives of investigating the extent to which their individual estimates of breast cancer risk are consistent with each other, and helping to identify the confounding or effect-modifying roles of other variables. In these analyses the observations analysed are the (summarized) results of each individual study, the unit of analysis being a study or a subgroup therein rather than a person within a study, and the influence of the characteristics of a study on the results therein can be investigated directly.

Method

As complete a list as possible of published comparative epidemiological studies of OC use and the risk of breast cancer published between 1980 and 1989 was compiled through literature searches and informal contacts. All of the studies identified are included in each meta-analysis reported here unless (i) the study did not include specific results for the subgroup of interest in the meta-analysis, (ii) the study results are represented in another paper which is already included in the meta-analysis or (iii) insufficient details of the study were available. Thus the number of studies included varies between the meta-analyses reported: 20 in analyses by age group, 13 by parity and 24 by duration of use.

As far as possible, a single, common set of definitions of outcome, explanatory and confounding variables compatible with those used in each of the individual studies was derived and used in coding the characteristics and results of the individual studies. Data summarizing the results of each study in respect of the relative risk of breast cancer in OC users in age, parity and duration of use subgroups were extracted. For some studies it was necessary to estimate key items of data not reported in the published account; numbers of cases and controls (or exposed and unexposed subjects) in subgroups of the study samples were most frequently estimated in this way.

Twenty-seven different sets of age at diagnosis categories, 11 parity categories, and 42 duration of use categories were employed in reporting the results of the various primary studies. These were allocated to the category in two standard sets [(i) <25, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55+ and (ii) <45, 45 and over] in which the majority of the reported subgroup fell, the parity categorizations to nulliparous or parous, and the total duration of OC use categories to <2, 2–4, 4–8, 8+ years.

Other study design characteristics were encoded, including type of study (case-control/cohort), place of study (UK/USA/other), source of study subjects (hospital/neighbourhood, or friend/resident list/GP list/family planning clinic/screening system/nurse occupational group), matching factors (whether year of interview, geographical area or hospital were used in matching or not), total number of matching factors used, method of data collection (personal interview/telephone interview/postal questionnaire), the year each study ended (1976–82, 1983–88), maximum and minimum ages at diagnosis, and marital status (all/ever married only), and race (all/white only) of the study samples. Some aspects of the analysis of study results were also encoded, including which adjustment factors were employed (age at diagnosis, age at first full term pregnancy, parity, age at menarche, family history of breast cancer, history of benign breast disease), total number of adjustment factors used, and method of standardization of study results (external/internal standard).

Variations of the estimates of relative risks between studies are described in weighted histograms (where the weights are the inverse of the variance) to reflect the precision of each estimate of relative risk (Kleinbaum *et al.* 1982). The summary data were analysed more formally by means of meta-regres-

Table 1. Basic characteristics of the studies

Study					Sample size							
No.	Author	Type	Place	Time period	Cases	Controls	Cohort	Source of cases/ exposed	Source of controls/ not exposed	Data collection method	Marital status	Race
1.	Paffenbarger *et al* (1980)	Case-control	USA	1970–77	1868	3391	N/A	Hospital	Hospital	Personal interview	All	All
2.	RCGP (1981)	Cohort	UK	1968–79	N/A	N/A	46000	GP list	GP list	Personal interview	Married	All
3.	Pike *et al* (1981)	Case-control	USA	1972–78	163	272	N/A	Cancer registry	N'bourhood/ friend	Telephone interview	All	White
4.	Trapido (1981)	Cohort	USA	1970–76	N/A	N/A	65939	Residents list	Residents list	Postal questionnaire	Married	All
5.	Brown (1981)	Cohort	USA	1968–77	N/A	N/A	14591	Health plan	Health plan	Personal interview	All	All
6.	Brinton *et al* (1982)	Case-control	USA	1973–77	963	858	N/A	Screening system	Screening system	Personal interview	All	White
7	Harris *et al.* (1982)	Case-control	USA	1977–78	112	469	N/A	Cancer registry	Residents list	Personal interview	All	White
8.	Vessey *et al* (1982)	Case-control	UK	1968–80	1176	1176	N/A	Hospital	Hospital	Personal interview	Married	All
9	Pike *et al* (1983)	Case-control	USA	1972–82	314	314	N/A	Cancer registry	N'bourhood/ friend	Telphone interview	All	White
10	Hennekens *et al* (1984)	Case-control	USA	1960–76	989	9890	N/A	Regd nurse	Regd nurse	Postal questionnaire	Married	All
11.	Rosenberg *et al* (1984)	Case-control	USA	1976–81	1191	5026	N/A	Hospital	Hospital	Personal interview	All	All
12.	Stadel *et al* (1985)	Case-control	USA	1980–82	2088	2065	N/A	Cancer registry	Telephone list	Personal interview	All	All
13.	La Vecchia *et al* (1986)	Case-control	Italy	1982–85	776	1282	N/A	Hospital	Hospital	Personal interview	All	All
14	Lipnick *et al* (1986)	Cohort	USA	1976–80	N/A	N/A	121964	Regd nurse	Regd nurse	Postal questionnaire	Married	All
15	Meirik *et al* (1986)	Case-control	Sweden/ Norway	1984–85	422	723	N/A	Cancer registry	Population register	Personal interview	All	All
16	Miller *et al* (1986)	Case-control	USA	1977–83	521	521	N/A	Hospital	Hospital	Personal interview	All	All
17	Paul *et al* (1986)	Case-control	NZ	1983–85	433	897	N/A	Cancer registry	Electoral roll	Telephone interview	All	All
18	Sattin *et al* (1986)	Case-control	USA	1980–82	4711	4676	N/A	Cancer registry	Residents list	Personal interview	All	All
19	McPherson *et al.* (1987)	Case-control	UK	1980–84	1125	1125	N/A	Hospital	Hospital	Personal interview	Married	All
20	Schlesselman *et al.* (1987)	Case-control	USA	1980–82	4731	4752	N/A	Cancer registry	Telphone list	Personal interview	All	All
21	Ravnihar *et al* (1988)	Case-control	Yugo	1980–83	534	1989	N/A	Hospital	Hospital	Personal interview	All	All
22	RCGP (1988)	Cohort	UK	1968–88	N/A	N/A	36000	GP list	GP List	Personal interview	Married	All
23.	Stadel *et al* (1988)	Case-control	USA	1980–82	2945	2646	N/A	Cancer registry	Telephone list	Personal interview	All	All
24.	Miller *et al* (1989)	Case-control	USA	1983–86	407	424	N/A	Hospital	Hospital	Personal interview	All	All
25.	UK NCSG (1989)	Case-control	UK	1982–85	755	755	N/A	Cancer registry	GP list	Personal interview	All	White
26.	Vessey *et al* (1989)	Cohort	UK	1968–87	N/A	N/A	17032	Fam. planning	Fam. planning	Personal interview	Married	White
27	Jick *et al* (1989)	Case-control	USA	1975–83	127	174	N/A	Health plan	Health plan	Telphone interview	All	All

Table 2. Matching factors in selection of study samples

Study	Age	Marital status	Hospital/ geographical	Year of interview or year of diagnosis	Ethnic group	Parity	Age at end of education
Case-control studies							
Paffenbarger *et al* (1980)	*			*	*		
Pike *et al* (1981)	*		*		*		
Brinton *et al* (1982)†	*		*	*	*		
Harris *et al* (1982)†	*				*		
Vessey *et al* (1982)	*	*	*			*	
Pike *et al* (1983)	*		*		*		
Hennekens *et al* (1984)†	*						
Rosenberg *et al* (1984)	*						
Stadel *et al* (1985)	*		*	*			
La Vecchia *et al* (1986)	*						
Meirik *et al* (1986)	*		*				
Miller *et al.* (1986)	*		*	*			
Paul *et al* (1986)	*						
Sattin *et al* (1986)	*						
McPherson *et al* (1987)	*	*	*				
Schlesselman *et al* (1987)	*		*	*			
Ravnihar *et al* (1988)	*		*	*			
Stadel *et al.* (1988)	*		*	*			
Miller *et al* (1989)	*		*	*			
UK NCSG (1989)†	*				*		
Jick *et al* (1989)†	*						
Cohort studies							
Brown (1981)	*						
RCGP (1981)	*	*					
Trapido (1981)	*		*	*		*	*
Lipnick *et al* (1986)	*	*	*				
RCGP (1988)	*	*					
Vessey *et al* (1989)	*	*			*		

†Other matching factors: length of continuation in screening project (Brinton *et al.* 1982, Jick *et al* 1989); menopausal status (Hennekens *et al* 1984); same GP as case (UK NCSG 1989); not specified (Harris *et al* 1982)

sion techniques (Greenland 1987). The logarithms of the best estimates of relative risk available from each study were regressed on exposure, confounding and other explanatory variables, using a normal least-squares model, with a weight function proportional to the precision of each risk estimate, by means of the GLIM statistical package (Baker & Nelder 1986). The weight is the inverse of the variance of the log (relative risk) (Kleinbaum *et al* 1982). Three main sets of meta-analyses were performed, to explore variations of risk with (i) age at diagnosis, (ii) parity, and (iii) total duration of OC use, since different subsets of study reports included the risk estimates required for each set. The influence of individual studies was checked and sensitivity analyses performed where data encoding was problematical.

Results

Basic characteristics of the studies reported in the 27 papers analysed here are shown in Table 1, in order of publication year. There were 21 case-control studies and six cohort studies; 17 studies were carried out in the USA, six in the UK and four elsewhere. Study periods in the various studies included years between 1968 and 1988. There are wide differences in some studies between the numbers eligible for study and the numbers included; reasons cited for not including potential cases or controls included refusal of either patient or physician, death, inaccessibility and non-response. In eight of the studies both the cases and comparison group were obtained from hospitals. Of the 10 studies where the cases were obtained from cancer registries, seven obtained the comparison group from residents lists or electoral rolls. The data were collected by personal interview in 20 studies, by telephone interview in four and by postal questionnaire in three studies. Eight studies restricted their study populations to women who were married, ever married or living as married, and six considered only white women.

Table 2 shows for each of the 27 studies the matching factors reported to have been used in selection of the study populations. All studies, apart from one study by Harris *et al* (1982) which did not specify any matching factors, matched for age at diagnosis in some way. Matching for hospital or geographical area and to a lesser extent for the year of interview or diagnosis was common.

Table 3 shows the adjustment factors used in analyses carried out in the 27 studies. The factors for which adjustment was most often reported to have been made were age at diagnosis or selection, age at first full term-pregnancy, parity, and age at menarche, and less often, menopausal status, family history of breast cancer and history of benign breast cancer. The matching factors shown in Table 3 for each study were not, however, always used in *all* of the analyses presented in the reports. In some studies, matching on some factors was

Table 3. Adjustment factors used in studies

Study	Age at diagnosis or selection	Age at first full term pregnancy	Parity	Age at menarche	Menopausal status	Family history of breast cancer	History of benign breast disease or breast biopsy	BMI or weight	Social class	Smoking
Case-control studies										
Paffenbarger *et al* (1980)†	*	*			*					
Pike *et al* (1981)			*	*		*	*			
Brinton *et al* (1982)	*				*					
Harris *et al* (1982)†	*	*	*	*	*					
Vessey *et al* (1982)†		*		*	*	*	*		*	*
Pike *et al* (1983)	*	*								
Hennekens *et al* (1984)	*	*	*			*				
Rosenberg *et al* (1984)†	*	*	*	*	*	*	*	*		
Stadel *et al* (1985)†	*	*	*			*	*			
La Vecchia *et al* (1986)†	*	*	*	*				*	*	*
Meirik *et al* (1986)†		*	*	*	*	*	*			
Miller *et al* (1986)†	*	*	*	*	*	*	*	*		
Paul *et al* (1986)†	*	*		*		*	*			
Sattin *et al* (1986)†	*	*	*		*	*	*	*		
McPherson *et al* (1987)		*	*	*	*	*	*		*	*
Schlesselman *et al* (1987)	*			*						*
Ravnihar *et al* (1988)†	*	*		*	*	*	*			
Stadel *et al* (1988)	*		*	*		*				
Miller *et al* (1989)†	*	*	*	*	*	*	*	*		
UK NCSG (1989)†	*	*	*	*		*		*		*
Jick *et al* (1989)†	*	*		*		*	*			
Cohort studies										
Brown (1981)†	*		*							*
RCGP (1981)	*		*						*	*
Trapido (1981)	*									
Lipnick *et al* (1986)†	*	*	*	*	*	*	*	*		
RCGP (1988)	*		*						*	*
Vessey *et al* (1989)	*	*			*					

†Other adjustment factors: race, education, age at first marriage, age at menopause (Paffenbarger 1980), history of other cancer, education (Harris 1982), alcohol consumption (Vessey 1982), geographic area, year of interview, years of education, number of lifetime hospital admissions, religion, alcoholism, age at menopause, ethnic group, type of OC (Rosenberg 1984), frequency of breast examination (Stadel 1985); marital status, education, age at menopause, non OC female hormone use (La Vecchia 1986), total duration of OC use (Meirik 1986), race, marital status, previous admissions, alcohol consumption, education, religion, age at menopause (Miller 1986), ethnic group (Paul 1986), area of residence, education, number of ovaries, age at last menstrual period, postmenopausal oestrogen therapy, indexes of medical care (Sattin 1986), alcohol consumption (McPherson 1987); years of schooling (Ravnihar 1988); geographic area, interview year, alcohol use, years of education, religion, non obstetric hospital visits (Miller 1989), region of residence, marital status, age at leaving school, alcohol consumption, breast feeding, type of OC (UK NCSG 1989); education, OC use (never, past, current) (Brown 1981); type of menopause, age at menopause (Lipnick 1986)

reported to be unnecessary, and in others separate analyses by subgroups complemented the matching procedure.

In Fig. 1, a (precision) weighted histogram of relative risk estimates by age at diagnosis is shown, with the results for subgroups aged <45 years and ≥45 years at diagnosis being separately identified. The main weight of evidence lies at relative risks close to unity, although a considerable range of estimates is apparent. There is a weak suggestion that higher relative risks are to be found in the younger age group. Weighted histograms of relative risk by duration of OC use and by parity showed similar patterns.

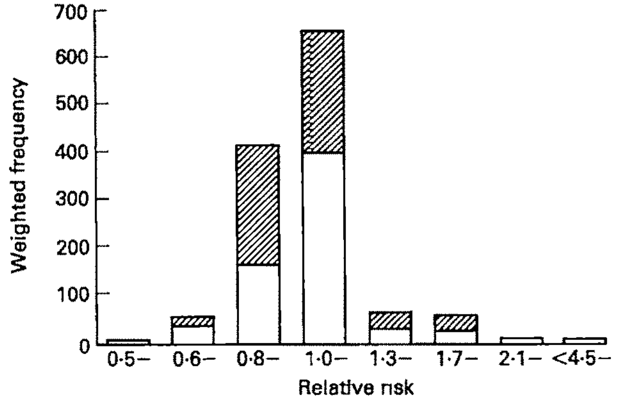


Fig. 1. Precision-weighted histogram of estimates of relative risk of breast cancer with oral contraceptive use, by age at diagnosis subgroup. (▨, ≥45 years; □, <45 years).

Funnel plots of the overall relative risk estimates for each study versus the precision of these estimates showed greater variability in studies of smaller sample size (and lower precision) with relative risk estimates converging to values slightly above one. There was no obvious shortfall of reported results in the region close to a relative risk of one in smaller studies; such a shortfall would be expected if publication bias were important (Greenland 1987) unless mediated through publication of subgroup-specific results. Fig. 2 shows the relative risks by age group within the study by date of publication, with results allocated where necessary to the standard age group in which the majority of members of the reported age group falls. A tendency for relative risks reported in some subgroups in later studies to be raised can be discerned; this is investigated by more formal meta-analytic methods below.

The base (null) models, in which no explanatory variables were included, were fitted for each of the main groups of analysis, I–III. These yield an overall estimate of the relative risk of breast cancer with OC use of 1·10, with 95% CI 1·04 to 1·17 in the subgroup of studies subsequently analysed for age at diagnosis variations (analysis I); 1·06, with 95% CI 0·99 to 1·15 (parity subgroup, II); and 1·13, with 95% CI 1·07 to 1·19 (duration of OC use subgroup, III).

A marked improvement of fit was obtained in some or all of the subgroups I–III when a single term reflecting the source of

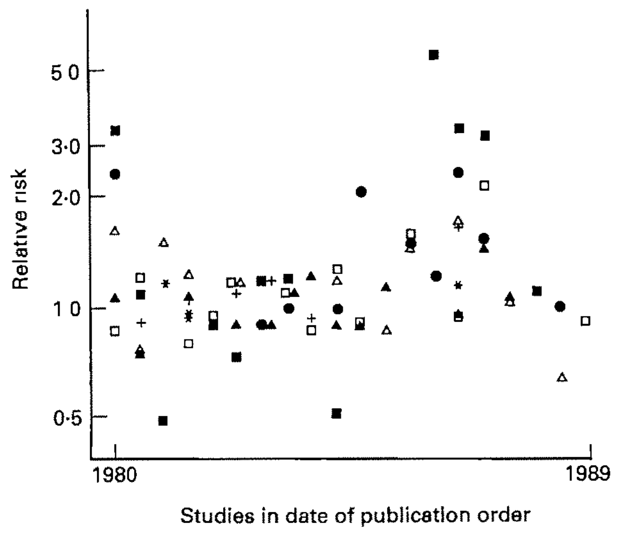


Fig. 2. Relative risks by age group in each study, in year of publication order. Standard age groups: (●) 25–29, (■) 30–34, (□) 35–39, (▲) 40–44, (△) 45–49, (+) 50–54, (*) 55+

subjects, data collection method, use of geographical area as a matching factor, number of factors for which adjustment was made in the study analysis, the calendar period in which the study ended, marital status and race was included in the model. Age at diagnosis, parity, and duration of use variables improved the fit in analyses I, II and III respectively. Table 4 presents relative risk estimates and 95% CI from the single explanatory variable models which lead to a marked improvement of fit in one or more of the analyses I–III. Variations with type and place of study are also shown despite the relatively poor fit of these models. Studies which included women of all types of marital status appeared to have higher estimated relative risks than those only including married women, and the estimated relative risk was similarly higher in studies in which data collection was by personal interview rather than postal questionnaire or telephone interview. General practice lists as a source of study subjects, matching for area or hospital and a recent end of study date (as in Fig. 2 above) are all associated with the highest estimated relative risks. Interpretation of these differentials should, however, be cautious in view of the lack of fit of these models. Substantial between-study heterogeneity remained unexplained; the best fitting model, that for source of subjects in analysis III, accounted for only 11% of the total residual sum of squares.

In the analysis (I) by age at diagnosis, inclusion of the key age term alone significantly improved the fit of the model, giving an estimated relative risk of 1·16 (95% CI 1·07–1·25) for the <45 years group, and 1·03 (95% CI 0·94–1·13) for the ⩾45 category. Use of the alternative 8-category classification suggests that risk is greatest in the 30–34 age group, the esimate being 1·25 (95% CI 1·04–1·50). In the analyses (II) by parity the estimated relative risk for nulliparous women was 1·21 (95% CI 0·99–1·47) and for parous women was 1·03 (95% CI 0·95–1·13). A term reflecting total duration of OC use significantly improved the fit of models in analyses (III) with a steady increase in estimated relative risk from 1·04 (95% CI 0·94–1·16) for durations of <2 years to 1·27 (95% CI 1·12–1·44) for >8 years use.

More complex models comprising two or more explanatory variables, including interaction terms to allow for variations of the effect of other variables between the age, parity and duration of use groups were also fitted. These more complex models were again unable to explain between-study heterogeneity fully. Lack of data in several categories defined by combinations of explanatory variables prevented exploration of some potentially useful models.

Variables identifying sources of subjects and the date of study showed strong interactions with age in analyses I. The highest relative risk estimates were in the younger age groups in studies with the most recent end dates. Results for models including terms for study end date and source of cases as well as an age group term are shown in Table 5. In general, the improvement of fit of corresponding models in analyses II and III and interaction effects therein were weak.

Discussion

In broad terms the findings of the meta-analyses accord with the conclusions of previous (narrative) reviews of studies of breast cancer risk following oral contraceptive use. Clear-cut results in variations of risk with age at diagnosis, parity and duration of OC use are obstructed by the inconsistencies between studies in the categories of these variables used or reported. Breast cancer risk is, however, apparently somewhat raised in the younger age groups (those below rather than above 45, and perhaps especially those in their thirties), as already suggested (Stadel *et al.* 1988). Breast cancer risk increases with increasing duration of OC use, is raised in nulliparous women, and varies with some other variables relating to aspects of study design, notably source of subjects, place of study and method of data collection. None of these increases is substantial, and the findings of an overview are inevitably less extreme than those of some of the individual studies it includes.

Models comprising terms reflecting source of subjects, their marital status, the type of study, data collection methods, matching for geographical area, the number of adjustment factors used in the study analysis, the country of study and the calendar period in which the study ended all demonstrated differentials in risk. The interaction of age and study date effects, although again not an entirely clear-cut effect, could result from a pattern of risk which varies between cohorts of OC users and with length of follow-up, or from an improving quality of studies over time, although over-interpretation of interaction effects should be avoided (Early Breast Cancer Trialists' Collaborative Group 1990). Study quality is an important issue, but definition of a quality of epidemiologial studies is more difficult than for clinical trials, where randomization, blindness, etc., provide relatively clear criteria of quality. Use of criteria suggested for epidemiological studies (Elwood 1988; Lichtenstein *et al* 1987) would need to be supported by a substantial sensitivity analysis exercise.

There has been much speculation in earlier reviews about the role of variations of data collection methods, sources of subjects and place of study, with repeated emphasis on the importance of unidentified sources of bias. Some but not all sources of bias in and variation between the various studies are identifiable. For example, non-response biases may be impor-

Table 4. Relative risk of breast cancer with oral contraceptive use: estimates and 95% confidence intervals from single explanatory variable models

	Analysis					
	I Age at diagnosis		II Parity		III Total duration of OC use	
Variable	RR	95% CI	RR	95% CI	RR	95% CI
Sources of cases/exposed						
Hospital	1·10	0·99–1·22	1·12	0·93–1·35	1·15	1·03–1·38
Cancer registry	1·20	1·07–1·34	1·06	0·94–1·19	1·17	1·08–1·27
Residents list	0·87	0·65–1·15	0·91	0·63–1·30	0·86	0·63–1·17
Registered nurses	1·04	0·90–1·19	1·01	0·81–1·27	1·02	0·89–1·16
GP lists	1·39	1·08–1·80	1·14	0·76–1·71	1·25	1·00–1·57
Family planning clinics/health plan	0·94	0·76–1·16	not estimated		0·93	0·69–1·26
Screening	1·08	0·80–1·45	1·10	0·77–1·58	1·05	0·78–1·40
Source of controls/unexposed						
Hospital	1·10	0·99–1·22	1·12	0·93–1·34	1·15	1·06–1·26
Neighbourhood/friend	not estimated		not estimated		1·59	1·22–2·06
Population/electoral/resident list	1·12	1·00–1·25	1·04	0·93–1·16	1·10	1·01–1·20
Registered nurses	1·04	0·90–1·19	1·01	0·81–1·27	1·02	0·89–1·16
GP lists	1·36	1·13–1·63	1·18	0·86–1·62	1·28	1·07–1·53
Family planning clinics/health plan	0·94	0·76–1·16	not estimated		0·93	0·69–1·26
Screening	1·08	0·80–1·46	1·10	0·77–1·58	1·05	0·79–1·40
Marital status						
All	1·16	1·08–1·25	1·08	0·99–1·18	1·16	1·10–1·23
Married only	0·99	0·90–1·10	0·92	0·74–1·15	1·01	0·91–1·13
Race						
All	1·11	1·04–1·18	1·05	0·97–1·15	1·11	1·05–1·17
White only	1·09	0·93–1·29	1·15	0·88–1·49	1·26	1·10–1·44
Data collection method						
Personal interview	1·15	1·07–1·23	1·11	1·01–1·21	1·16	1·09–1·23
Telephone interview	0·90	0·67–1·20	0·71	0·49–1·04	1·15	0·96–1·37
Postal questionnaire	1·00	0·88–1·14	0·98	0·53–1·83	0·99	0·87–1·12
Number of adjustment factors used in analysis of study						
Increment per factor	1·00	0·99–1·02	1·03	1·00–1·05	1·00	0·98–1·01
Matching for geographical area/hospital						
Matched	1·18	1·09–1·28	1·09	0·99–1·21	1·19	1·11–1·28
Not matched	1·03	0·94–1·12	1·01	0·88–1·15	1·06	0·98–1·14
Study end year						
1976–82	0·98	0·89–1·09	1·03	0·94–1·14	1·07	0·98–1·17
1983–88	1·16	1·08–1·25	1·13	0·97–1·50	1·16	1·09–1·23
Type of study						
Case-control	1·12	1·05–1·20	1·07	0·98–1·17	1·14	1·08–1·21
Cohort	1·03	0·92–1·19	1·00	0·77–1·31	1·05	0·92–1·19
Place of study						
UK	1·06	0·94–1·19	1·00	0·77–1·29	1·09	0·96–1·24
USA	1·11	1·03–1·19	1·07	0·97–1·17	1·12	1·06–1·20
Other	1·20	1·00–1·44	1·03	0·80–1·32	1·19	1·03–1·38

tant, but they can only be identified and quantified if adequately reported. Hence, even taken together, the explanatory variables studied are able to account for only a minor proportion of the observed variation in estimates from the various studies. Some important issues of interpretation may not, however, be easily identifiable in this way. For example, the raised risk in nulliparous women remained when attention was restricted to the studies which included married women only, but the nulliparous subgroup of the married and of other marital status groups may differ importantly. Place of study is of interest due to the differing practices of OC use between the countries, particularly the longer use of high oestrogen pills in the USA, although in fact place was a weak explanatory factor in these meta-analyses. Most of the studies reported were case-control studies and this type of study tended to yield higher relative risk estimates than cohort studies.

Most of the studies report that they used a 'standard' method of analysis to take account of matching and possible confound-

Table 5. Relative risk of breast cancer with oral contraceptive use: estimates and 95% confidence intervals in selected models including several explanatory variables and interaction terms*

	Age <45 years		Age ≥45 years	
	RR	95% CI	RR	95% CI
(a) Age group, year of end of study and interaction terms				
(147·4 on 110 df)				
Study ending				
1982 or earlier	0·90	0·77–1·05	1·06	0·92–1·22
1983 or later	1·25	1·15–1·36	1·00	0·89–1·12
(b) Age group, source of cases and interaction terms				
(130·4 on 100 df)				
Source of cases/exposed				
Hospital	1·30	1·11–1·52	0·98	0·86–1·11
Cancer register	1·26	1·13–1·41	0·81	0·58–1·14
Residents list	0·93	0·63–1·38	0·81	0·54–1·22
Registered nurses	0·94	0·78–1·14	1·14	0·90–1·45
GP list	1·19	0·85–1·65	1·71	1·14–2·56
Family planning clinic	0·90	0·71–1·16	1·01	0·68–1·50
Screening system	1·00	0·57–1·75	1·11	0·77–1·60

*Residual sum of squares of null model: 172·8 on 113 degrees of freedom.

ing variables but give little detail. Differences in relative risk estimates of breast cancer and OC use between studies may be partly due to differences in adjustment methods between studies (Pike & Bernstein 1989) and the potential exists for induction as well as elimination of confounding bias by matching (Rothman 1986). Although coding may have failed to capture the full complexity of variations in study design and procedures, such as matching and adjustment procedures, the total number of adjustment factors employed in studies was found to have some explanatory value in the present meta-analyses. In some studies, however, adjustment for particular factors may not have been performed if it did not affect results obtained. Further, the desirability of adjustment for at least one factor—history of benign breast disease—is open to question.

Overall, these meta-analyses suggest that risks of breast cancer may be raised somewhat in OC users, with risks increased by around 20% in younger, nulliparous and long use duration subgroups. However, most of the data thus reviewed relate to the use of older, higher dose of OCs, and it is reasonable to assume that the risks associated with current low dose OCs will be lower. Further, in any overall assessment, the risks of OC use need to be considered along with protective effects, including those against ovarian and endometrial cancers.

The importance of several design factors which must be considered carefully in planning future studies in this field if they are to contribute usefully to the overall picture is highlighted. Meta-analytic techniques allow assessment of the potential impact of further studies through the use of simulation techniques, and provide a well-defined basis on which sequential and quantitative review of studies in this field can be built as reports (Paul *et al.* 1990; World Health Organization Collaborative Group on Neoplasia and Steroid Contraception 1990) of results of new studies accrue.

Acknowledgments

This work was supported by a grant from the Department of Health. We thank Martin Vessey, Sue Wood and other members of the Committee on Safety of Medicines and the Medicines Control Agency for their help and encouragement.

References

Altman, D. G. & Elbourne, D. (1988) Commentary: combining results from several clinical trials. *Br J Obstet Gynaecol* **95,** 1–2.

Anonymous (1985) Another look at the pill and breast cancer (Editorial). *Lancet* **ii,** 985–987.

Baker R. J. & Nelder J. A. (1986) The GLIM System Release 3·77 Manual. Numerical Algorithms Group, Oxford.

Bracken M. B. (1990) Oral contraception and congenital malformations in offspring: a review and meta-analysis of the prospective studies. *Obstet Gynecol* **76,** 552–557.

Brinton L. A., Hoover R., Szklo M., Fraumeni J. F (1982) Oral contraceptives and breast cancer. *Int J Epidemiol* **11,** 316–322.

Brown W. (1981) Infective and parasitic diseases; malignant neoplasms; benign neoplasms. In *The Walnut Creek Contraceptive Drug Study Vol III.* NIH Publication No. 81–564 Center for Population Research Monograph, ch. 3.

Clavel F., Benhamou E., Sitruk-Ware R., Mauvais-Jarvis P. & Flamant R. (1985) Breast cancer and oral contraceptives. a review. *Contraception* **320,** 553–559.

Early Breast Cancer Trialists' Collaborative Group (1990) *Treatment of Early Breast Cancer. Vol I: Worldwide Evidence 1985–1990.* Oxford University Press, Oxford, p 8.

Elwood J M. (1988) *Causal Relationships in Medicine,* Oxford University Press, Oxford.

Ewertz M., Duffy S. W., Adami H. -O. *et al.* (1990) Age at first birth, parity and risk of breast cancer: a meta-analysis of eight studies from the Nordic countries. *Int J Cancer* **46,** 597–603.

Greenland S. (1987) Quantitative methods in the review of epidemiological literature. *Epidemiol Rev* **9,** 1–30.

Harris N. V., Weiss N. S., Francis A. M. & Polissar L (1982) Breast cancer in relation to patterns of oral contraceptive use. *Am J Epidemiol* **116,** 643–651.

Hennekens C. H., Speizer F. E., Lipnick R. J. *et al* (1984) A case-control study of oral contraceptive use and breast cancer. *J Natl Cancer Inst* **72,** 39–42

Jick S. S., Walker A M., Stergachis A. & Jick H. (1989) Oral contraceptives and breast cancer. *Br J Cancer* **59,** 618–621.

Kleinbaum D. G., Kupper L. L. & Morgenstern H. (1982) *Epidemiologic Research: Principles and Quantitative Methods.* Lifetime Learning Publications, Belmont.

La Vecchia C., Decarli A., Fasoli M. *et al.* (1986) Oral contraceptives and cancers of the breast and of the female genital tract. Interim results from a case-control study. *Br J Cancer* **54,** 311–317.

Lichtenstein M . J., Mulrow C D. & Elwood P. C. (1987) Guidelines for reading case-control studies *J Chron Dis* **40** , 893–903

Lipnick R. J , Buring J. E , Hennekens C. H *et al* (1986) Oral contraceptives and breast cancer a prospective cohort study. *JAMA* **255,** 58–61.

McPherson K. & Drife J. O. (1986) The pill and breast cancer: why the uncertainty? (Editorial). *Br Med J* **293,** 709–710.

McPherson K., Vessey M. P, Neil A., Doll R., Jones L & Roberts M. (1987) Early oral contraceptive use and breast cancer: results of another case-control. *Br J Cancer* **56,** 653–660.

Meirik O , Lund E , Adami H. O., Bergstrom R., Christofferson T. & Bergsjo P. (1986) Oral contraceptive use and breast cancer in young women. A joint national case-control study in Sweden and Norway. *Lancet* **ii,** 650–653.

Miller D R., Rosenberg L , Kaufman D. W., Schottenfeld D., Stolley

P. D. & Shapiro S. (1986) Breast cancer in relation to early contraceptive use. *Obstet Gynecol* **68,** 863–868.

Miller D. R., Rosenberg L ., Kaufman D. W., Stolley P. D., Ellen Warshauer M. & Shapiro S. (1989) Breast cancer before age 45 and oral contraceptive use: new findings. *Am J Epidemiol* **129,** 269–280.

Paffenbarger R. S , Kampert J. B. & Chang H. G. (1980) Characteristics that predict risk of breast cancer before and after the menopause. *Am J Epidemiol* **112,** 258–268.

Paul C., Skegg D. C. G., Spears G. F. S. & Kaldor J M. (1986) Oral contraceptives and breast cancer: a national study. *Br Med J* **293,** 723–726.

Paul C., Skegg D. C. G. & Spears G F. S. (1990) Oral contraceptives and risk of breast cancer. *Int J Cancer* **46,** 366–373

Pike M. C. & Bernstein L. (1989) Oral contraceptives and breast cancer. *Lancet* **ii,** 615–616.

Pike M. C., Henderson B. E., Casagrande J. T., Rosario I. & Gray G. E. (1981) Oral contraceptive use and early abortion as risk factors for breast cancer in young women. *Br J Cancer* **43,** 72–76.

Pike M. C., Henderson B. E., Krailo M. D., Duke A. & Roy S. (1983) Breast cancer in young women and the use of oral contraceptives: possible modifying effect of formulation and age at use. *Lancet* **ii,** 926–930.

Ravnihar S., Primic Zakelj M., Kosmelj K. & Stare J. (1988) A case-control study of breast cancer in relation to oral contraceptive use in Slovenia. *Neoplasia* **35,** 109–121.

Risch H A. (1988) A unified framework for meta-analysis by maximum likelihood. *Am J Epidemiol* **128,** 906.

Rosenberg L., Miller D. R., Kaufman D. W., Helmrich S., Stolley P. D., Schottenfeld D. & Shapiro S. (1984) Breast cancer and oral contraceptive use. *Am J Epidemiol* **119,** 167–176.

Rothman K. J. (1986) *Modern Epidemiology, ch 13,* Little, Brown & Co , Boston, Toronto.

Royal College of General Practitioners (1981) Breast cancer and oral contraceptives: findings in Royal College of General Practitioners Study. *Br Med J* **282,** 2089–2092.

Royal College of General Practitioners (1988) Breast cancer and the pill—a further report from the Royal College of General Practitioners' oral contraceptive study *Br J Cancer* **58,** 676–680.

Sackett D. L (1979) Bias in analytic research. *J Chron Dis* **32,** 51–63.

Sattin R. W., Rubin G. L., Wingo P. A , Webster L. A. & Ory H.W. (1986) Oral contraceptive use and the risk of breast cancer. *New Engl J Med* **315,** 405–411.

Schlesselman J. J., Stadel B. V., Murray P., Wingo P. A. & Rubin G. L. (1987) Consistency and plausibility in epidemiologic analysis: application to breast cancer in relation to use of oral contraceptives *J Chron Dis* **40,** 1033–1039.

Stadel B. V., Lai S., Schlesselman J. J. & Murray P. (1988) Oral contraceptives and premenopausal breast cancer in nulliparous women. *Contraception* **38,** 287–299.

Stadel B. V, Rubin G. L., Webster L. A , Schlesselman J. J. & Wingo P. A. (1985) Oral contraceptives and breast cancer in young women. *Lancet* **ii,** 970–973.

Trapido E. J. (1981) A prospective cohort study of oral contraceptives and breast cancer. *J Natl Cancer Inst* **67,** 1011–1015.

UK National Case-control Study Group (1989) Oral contraceptive use and breast cancer risk in young women. *Lancet* **i,** 973–983.

Vessey M. P. (1986) Oral contraceptives and breast cancer. *IPPF Medical Bulletin* **21,** 1–2.

Vessey M. P., McPherson K.. Yeates D. & Doll R. (1982) Oral contraceptive use and abortion before first term pregnancy in relation to breast cancer risk. *Br J Cancer* **45,** 327–331.

Vessey M. P., McPherson K., Villard-Mackintosh L. & Yeates D. (1989) Oral contraceptives and breast cancer: latest findings in a large cohort study. *Br J Cancer* **59,** 613–617.

World Health Organization Collaborative Group on Neoplasia and Steroid Contraception (1990) Breast cancer and combined oral contraceptives: results from a multinational study The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. *Br J Cancer* **61,** 110–119.

Received 28 March 1991
Accepted 10 September 1991

British Journal of Obstetrics and Gynaecology
March 1992, Vol. 99, pp. 247–252

REPRODUCTIVE SCIENCE

Renal sodium retention does not occur during the luteal phase of the menstrual cycle in normal women

D. L. BISSON
Research Registrar in Obstetrics and Gynaecology
G D. DUNSTER
Consultant Obstetrician and Gynaecologist
J. P. O'HARE
Consultant Physician
The Wolfson Centre
Royal United Hospital, Bath
D. HAMPTON
Senior Biochemist
M. D. PENNEY
Consultant Chemical Pathologist
Department of Chemical Pathology,
Royal Gwent Hospital, Newport

ABSTRACT

Objective To determine whether weight gain due to renal sodium and water retention occurs in the luteal phase of the normal menstrual cycle.

Design Prospective observational study.

Setting Research laboratory installed with modified spa bath.

Subjects Ten normal healthy women.

Intervention Each subject underwent two experiments, one in each phase of the menstrual cycle, involving 3 h head-out water immersion and a pre- and post immersion control hour. 25 ml blood samples were obtained every hour before, during and after water immersion.

Main outcome measures Renal and hormonal responses to water immersion during the luteal and proliferative phases of the cycle.

Results There was no change in weight, creatinine clearance, basal sodium excretion or plasma atrial natriuretic peptide between the two phases of the cycle. There was a significant rise in basal progesterone, plasma aldosterone and plasma renin activity in the luteal phase of the ovulatory cycles. Renal and hormonal responses to immersion including sodium and calcium excretion, elevation of atrial natriuretic peptide (ANP) and suppression of plasma aldosterone and plasma renin activity were identical in the two phases of the menstrual cycle.

Conclusion We found no evidence to support the hypothesis that renal sodium and water retention occurs in the luteal phase of the normal menstrual cycle.

Despite extensive research spanning over 50 years, the question of whether sodium and water retention occurs in the luteal phase of the normal menstrual cycle remains unresolved. The hormonal changes which might contribute to the effect are well reported. Plasma progesterone, aldosterone and renin activity are elevated in the luteal phase of ovulatory cycles (Katz & Romfh 1972; Michelakis *et al.* 1975; Munday *et al* 1981; Brown *et al* 1964). Aldosterone and renin both induce renal sodium retention whilst progesterone antagonizes this effect (Landau & Lugibihl 1958).

Atrial natriuretic peptide (ANP) is released in response to volume induced stretch of the atrium, it antagonizes the renin-angiotensin system and generates a natriuresis and a diuresis (Hussain & O'Brien 1989). ANP levels do not appear to show any cyclical variation during the normal menstrual cycle (Jackson *et al* 1987; Tan *et al.* 1987, Davidson *et al* 1988; Hussain *et al* 1990) but a significant fall in ANP has been claimed in subjects with premenstrual syndrome (Hussain *et al.* 1990).

It has been reported that oestrogen therapy results in decreased urinary calcium excretion which has been observed both in women taking the oral contraceptive pill (Goulding & McChesney 1977) and in postmenopausal women on hormone replacement therapy (Young *et al.* 1968). The mechanism is unclear but may be due to inhibition of bone resorption and antagonism of parathyroid hormone (PTH). Studies of the relation of reproductive hormones and calcium metabolism during the menstrual cycle are limited but Pitkin *et al.* (1978) reported cyclical changes in ionized calcium, calcitonin and immunoreactive PTH which could result in variations in urinary calcium excretion during the menstrual cycle.

Immersion to the neck in water at 35°C produces a large hydrostatic pressure gradient in the sitting subject which acts to redistribute about 700 ml of blood from the limbs centrally to the thoracic compartment (Epstein 1978). This causes a diuresis, natriuresis and calciuresis without any measurable change in glomerular filtration (Epstein *et al* 1976). The volume expansion effect of water immersion on the renal tubule is thought to be hormonally mediated. The hormonal changes include a twofold increase in ANP (Anderson *et al.* 1986), a reciprocal decrease in plasma renin activity and plasma aldosterone (Epstein & Saruta 1971) and a decrease in arginine vasopressin (ADH) (O'Hare *et al* 1985).

Head out water immersion therefore provides a dynamic test of renal tubular function which has not been studied previously

Correspondence. Dr Dina L. Bisson, Department of Obstetrics, Southmead Hospital, Bristol BS10 5NB

during the two phases of the menstrual cycle in normal women. We have used this model to determine whether there was renal sodium or calcium retention in the luteal phase of the cycle.

Subjects and methods

Ten normal healthy women aged 18–30 (median 24·5) years were studied during the follicular (day 7–12) and luteal (day 19–25) phases of the same menstrual cycle. The women had regular menstrual cycles and were not taking any medication; none of them complained of symptoms suggestive of premenstrual syndrome and each completed a daily menstrual distress questionnaire. All subjects gave informed consent and the study was approved by the district ethics committee.

Sodium balance

Subjects were studied on their normal diets; each was asked to keep a record of her dietary intake on the 3 days preceding the first study and followed a similar diet before the second study to reduce within-subject variability in sodium excretion. This was then assessed by a 24 h urine collection immediately preceding each study.

Experimental protocol

After an overnight fast, the subject drank 400 ml of water at 0730 hours and arrived at the laboratory between 0830 and 0900 hours. On arrival she changed into suitable clothing, emptied her bladder, was weighed, drank 200 ml water and sat in a chair adjacent to the immersion tank for 60 min; 2·5 g of Emla cream (Astra Pharmaceuticals plc) containing 12·5 mg lignocaine and 12·5 mg prilocaine was applied to both antecubital fossae. After 55 min a cannula was inserted into an antecubital vein, 25 ml blood was withdrawn and the cannula was flushed with 1 ml Hepsal solution to maintain patency. The subject then emptied her bladder in the commode situated in the cubicle adjacent to the laboratory before entering and sitting in the water tank. The water level in the tank was adjusted to the level of the suprasternal notch and the water temperature was kept constant at 34·75 ± 0·25°C. The subject was given 200 ml of water to drink at the beginning of each hour to maintain hydration. At the end of each of the three subsequent hours of immersion, 25 ml blood was withdrawn and the subject left the tank briefly to empty her bladder. A further post immersion hour was spent seated near the tank during which lunch was given.

Preparation of samples

The 25 ml of blood was divided into chilled tubes, kept on ice and centrifuged at 4°C for 10 min before separation and freezing within 30 min. The samples were stored at –20°C.

Assay of samples

Serum sodium, potassium, creatinine and calcium were determined using a Technicon Chem 1 analyser. Urine sodium, potassium and creatinine were assayed using a Beckman Astra analyzer. Urinary calcium was assayed using a Cobas-Bio analyzer. Serum progesterone, plasma renin activity and plasma aldosterone were measured by standard radioimmunoassay techniques.

Atrial natriuretic peptide

Frozen plasma samples were transported to the Royal Gwent hospital in Newport and after extraction with Sep Pak C18 columns ANP was measured by a sensitive and specific radioimmunoassay using a monoclonal antibody (Prowse *et al* 1989). The overall mean recovery of ANP was 92·0 (SD 4·8) for 36 women and the detection limit for a 5 ml sample of plasma was 2 pg/ml. Between batch coefficient of variation for ANP was 13·3% at 30 pg/ml.

Statistical analysis

Basal values were compared using a paired *t*-test for normally distributed data or a Wilcoxon signed rank when the data were not normally distributed. If there was no difference in basal values, the responses to immersion were compared using a parametric ANOVA test with repeated measures (Greenhouse & Geisser 1959). Data were log transformed to normalize the distribution. When there was a difference in basal values the data were converted to relative changes to allow comparisons of the response to immersion to made between the two phases of the cycle using the parametric ANOVA test.

Results

There was no consistent weight change between the two phases of the cycle (see Table 1). None of the subjects had a positive Premenstrual Mood Index as assessed by the menstrual distress questionnaire (total premenstrual score minus preovulatory total) (O'Brien 1980).

Seven of the ten women ovulated as assessed by a six fold rise in the mid luteal phase serum progesterone level. Only the data from these seven women will be presented in the remainder of this paper. All results are expressed as mean (SE) unless otherwise stated.

24 h urinary volume and electrolytes

There were no significant differences in the 24-h urinary volume, creatinine clearance, absolute sodium or potassium excretion between the two phases of the menstrual cycle.

Sodium excretion

There was a two fold natriuresis in response to the immersion ($P<0{\cdot}001$) but no significant difference in response between the two phases of the cycle (f = 0·27) (Fig. 1).

Calcium excretion

There was a significant calciuresis maximal by the third hour of immersion ($P<0{\cdot}01$) but no significant difference in response between the two phases of the cycle (f = 0·12) (Fig. 2).

Hormonal changes

There was no significant difference in basal ANP levels in the

Table 1. Baseline data in the proliferative and luteal phases of the cycle in seven ovulating women

	Cycle phase		Significance*
	Proliferative	Luteal	t
Weight (kg)	51·9 (1·5)	51·8 (1·5)	0·48
24-h urinary volume (ml)	1000 (80)	1200 (150)	1·73
24-h urinary sodium (μmol/min)	69 (4)	73 (7)	0·39
24-h creatinine clearance (ml/min)	129 (10)	118 (8)	0·94
24-h urinary potassium (μmol/min)	40 (3)	43 (4)	1·05

*There was no significant difference between the two phases of the cycle for any of the variables.
Results are mean (SE) values.

two phases of the cycle and the level increased two fold during the second hour of immersion in both phases of the cycle (Fig. 3). Basal plasma renin activity and aldosterone were both considerably greater in the luteal phase of the cycle (Figs. 4 & 5). Both hormones were suppressed in response to immersion. To compare the two phases of the cycle, the percentage suppression was calculated and was approximately 70% for both hormones in either phase of the menstrual cycle. Plasma renin activity returned to basal levels by the end of the post immersion hour in both phases of the cycle but plasma aldosterone appeared to have a delayed recovery in the luteal phase of the cycle which may have been due to the elevated basal levels.

Discussion

It is received wisdom that normal women gain weight premenstrually due to renal sodium retention. This assumption is promoted by the advertising of various over-the-counter diuretics available without prescription but there is very little scientific evidence to support this viewpoint. Some studies (Thorn *et al* 1938; Okey & Stewart 1933; Sweeney 1934; Morton 1950; Thomas 1953; Janowsky *et al* 1973; Hassan Ahmad *et al.* 1990; Watson & Robinson 1965) have reported a cyclical change in weight but it is not consistently premenstrual and is often not repeated in subsequent cycles. In contrast, ten studies (Hussain *et al* 1990; Chesley & Hellman 1957; Andersch *et al.* 1978; Watts *et al.* 1985; Michelakis *et al.* 1971; Bruce & Russell 1962; Danforth *et al.* 1946; Golub *et al.* 1965; Taggart 1962; Abramson & Torghele 1961) reporting on a total of 199 subjects have shown no cyclical weight changes during normal menstrual cycles. In the present study we were unable to demonstrate any cyclical weight change and suggest that this is compatible with the findings in most other studies that are conducted carefully.

Table 2. Baseline hormonal changes in the proliferative and luteal phases in seven ovulating women

Hormone	Proliferative	Luteal	Significance P	t
Serum progesterone (nmol/l)	1·3 (0·4)	34·4 (2·4)	0·002	5·08
Plasma aldosterone (pmol/l)	310 (24)	1077 (202)	0·01	3·47
Plasma renin activity (ng/ml/h)	1.01 (0.1)	1·97 (0·4)	0·02	3·0
Atrial natriuretic peptide (pg/ml)	25 (5)	21 (2)	>0·05	1·02

Results are mean (SE) values.

In addition, the renal response to volume expansion was identical in the two phases of the cycle. If renal sodium retention was occurring in the luteal phase of the cycle one might expect an attenuated natriuretic response to volume expansion. Although the number of subjects in this study is limited, the responses for each individual were similar in both phases of the cycle. This study therefore provides evidence against the hypothesis that there is renal sodium retention leading to weight gain in the luteal phase of the normal menstrual cycle.

Previous studies on sodium and water changes during the normal menstrual cycle are extremely limited. Edwards & Bayliss (1973) using the effect of posture to induce volume depletion and a consequent decrease in diuresis, natriuresis and kaliuresis demonstrated a significantly greater decrease in the luteal phase of the cycle in eight normal women. By contrast, Michelakis (1971) showed no significant change in exchangeable sodium space during the menstrual phase compared with the rest of the cycle in six volunteers and Brochner-Mortensen *et al* (1987) showed no change in the extracellular fluid volume during the luteal phase of the cycle in 14 normal women.

We have confirmed that large changes in plasma renin activity and plasma aldosterone occur during the luteal phase of ovulatory cycles. The three anovulatory subjects who did not show a rise in serum progesterone had no change in basal plasma renin activity or plasma aldosterone. These data sup-

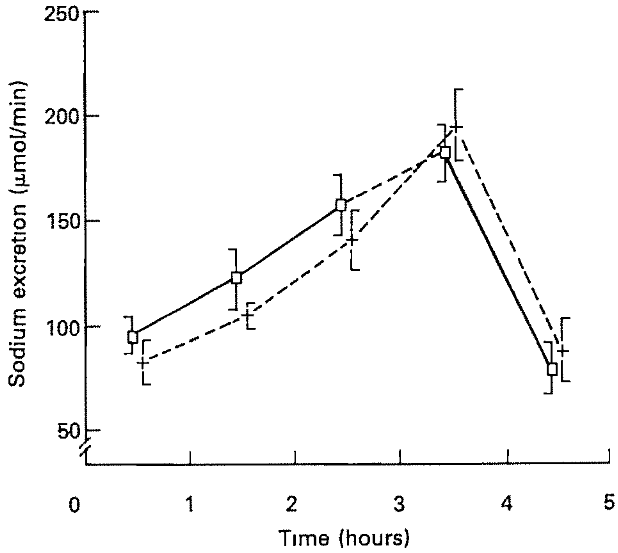


Fig. 1. Natriuretic response to water immersion for 3 h (hours 1–4) in the (□——□) proliferative phase and (+– – – –+) luteal phase of the menstrual cycle.

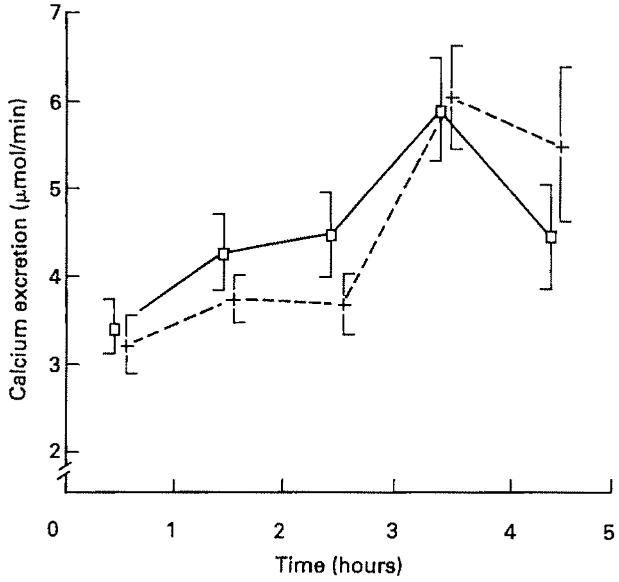


Fig. 2. Calciuretic response to water immersion for 3 h (hours 1–4) in the (□——□) proliferative phase and (+– – – –+) luteal phase of the menstrual cycle.

port the explanation that the rise in aldosterone and plasma renin activity in the luteal phase of the cycle is in response to the rise in progesterone. The progesterone stimulus to natriuresis and vasodilation may be inhibited by the activation of the renin-angiotensin-aldosterone system to maintain sodium homeostasis (Oparil *et al.* 1975). In addition our study has shown that, despite large basal increases in the luteal phase of the cycle, the responsiveness of these hormones to the stimulus of volume expansion remains intact which suggests that they are indeed reset around a higher baseline. This is comparable with the findings in pregnancy where elevated levels of renin and aldosterone occur in order to maintain sodium balance (Ehrlich 1982) and are regulated by normal volume control mechanisms (Weinberger *et al.* 1977).

We have shown that basal ANP levels are similar in the two phases of the normal menstrual cycle, in accord with previous work. The present study concerns the dynamic response to volume expansion and this has not been studied previously. ANP is known to rise in many situations where there is stimulation of the renin-angiotensin-aldosterone axis and may exert part of its effect by reducing renin secretion, blocking aldosterone secretion and inhibiting the sodium retaining action of aldosterone (Hussain & O'Brien 1989). This study has shown an identical response of ANP to volume expansion in both phases of

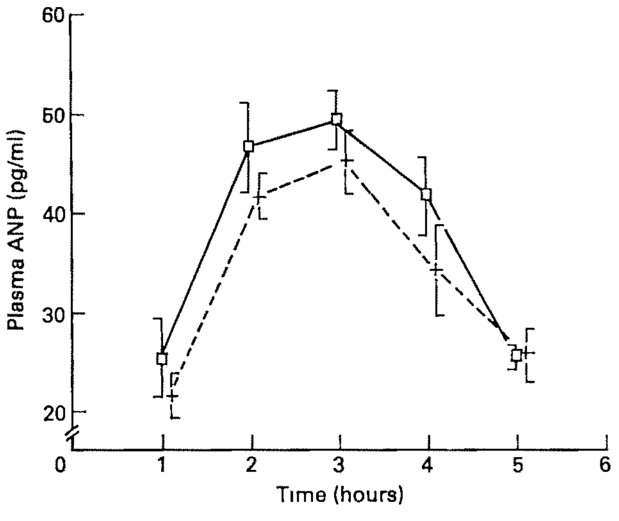


Fig. 3. Plasma atrial natriuretic (ANP) response to water immersion for 3 h (hours 1–4) in the (□——□) proliferative phase and (+– – – –+) luteal phase of the menstrual cycle.

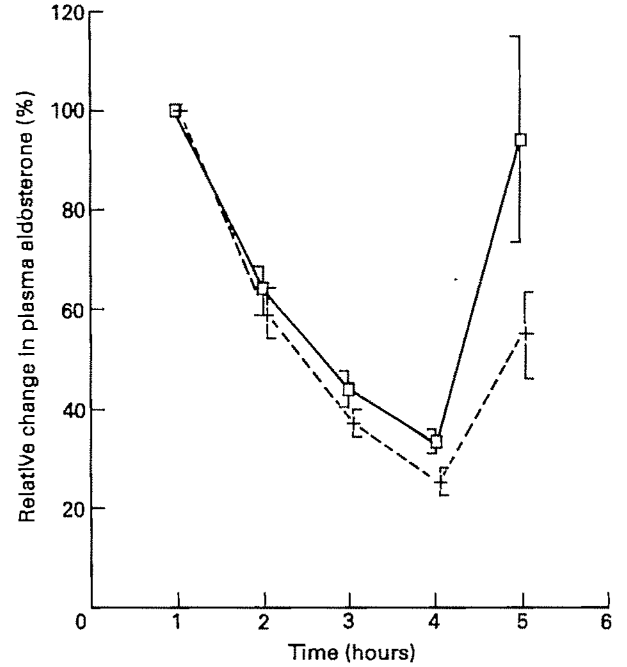


Fig. 4. Relative change in plasma aldosterone in response to water immersion for 3 h (hours 1–4) in the (□——□) proliferative phase and (+———+) luteal phase of the menstrual cycle.

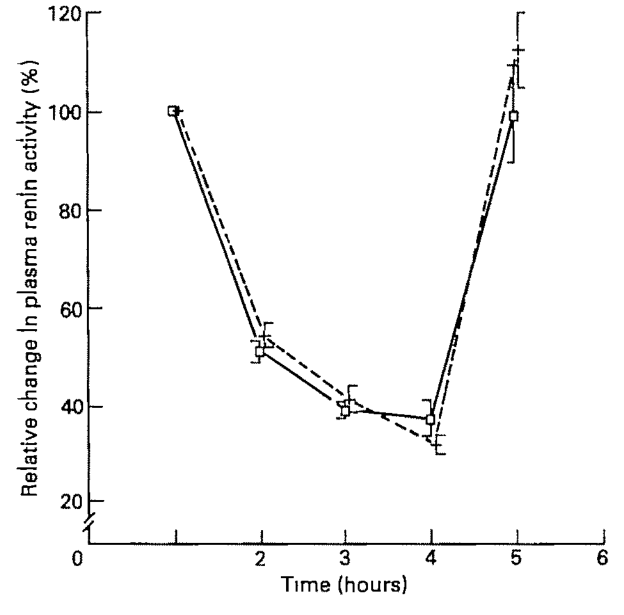


Fig. 5. Relative change in the plasma renin activity in response to water immersion for 3 h (hours 1–4) in the (□——□) proliferative phase and (+– – – –+) luteal phase of the menstrual cycle.

the menstrual cycle, with a dynamic rise that is the mirror image of the suppression of the renin-aldosterone axis.

Water immersion as a volume expansion stimulus produces a two-fold calciuresis. We have used this model to demonstrate that despite changes in reproductive hormones in the two phases of the cycle, there is no change in calcium excretion during volume expansion. The results of our study suggest that the hypocalciuric action of oestrogen is unlikely to be a direct renal effect on tubular calcium excretion but secondary to inhibition of bone resorption.

We would suggest that the symptoms of oedema and bloating reported by many women in the luteal phase of the cycle occur as a result of local hormonal changes affecting the capillaries with a redistribution of fluid to the interstitial compartment and not by any alterations in renal sodium or water balance. This might explain the lack of evidence for any weight increase from sodium retention and why medications such as diuretics which act on the kidney have not been shown to have any significant effect on premenstrual symptoms (Andersch 1978; O'Brien 1979) and may be harmful (MacGregor 1979).

Acknowledgments

D.L.B. was financed by a reseach grant from Wessex Regional Health Authority. We are grateful to Aquatech Ltd of Newbury for donating the spa bath and Radio Rentals for the audiovisual equipment. In addition we thank Mr D. Treby, Mrs Yvonne Cartwright and the laboratory staff of the Department of Biochemistry, Royal United Hospital, Bath for performing the electrolyte and serum progesterone assays and Mr J. Gooding of the Department of Chemical Pathology, Bristol Royal Infirmary for performing the plasma aldosterone and renin activity assays. ANP Antibody (ESA-4) was produced by Dr K. James (Edinburgh University) and Dr C. Prowse (Blood Transfusion) under a grant from the Quantum Fund, Edinburgh University.

References

Abramson M. & Torghele J. R. (1961) Weight, temperature changes and psychosomatic symptomatology in relation to the menstrual cycle. *Am J Obstet Gynecol* **81,** 223-232

Andersch B., Hahn L., Andersson M. & Isaksson B. (1978) Body water and weight in patients with premenstrual tension *Br J Obstet Gynaecol* **85,** 546-550.

Anderson J. V., Millar N. D , O'Hare J. P., MacKenzie J C. , Corrall R. J. M. & Bloom S. R. (1986) Atrial natriuretic peptide: physiological release associated with natriuresis during water immersion in man *Clin Sci* **71,** 319-322.

Brochner-Mortensen J., Paaby P., Fjeldborg P., Faffn K., Larsen C. E. & Moller-Petersen J. (1987) Renal haemodynamics and extracellular homeostasis during the menstrual cycle. *Scand J Clin Lab Invest* **47,** 829-835

Brown J. J., Davies D. L., Lever A. F. & Robertson J. I. S. (1964) Variations in plasma renin during the menstrual cycle. *Br Med J* **2,** 1114-1115

Bruce J. & Russell G F M. (1962) Premenstrual tension. A study of weight changes and balances of water, sodium and potassium. *Lancet* **ii,** 267-271.

Chesley L. C. & Hellman L. M. (1957) Variations in body weight and salivary sodium in the menstrual cycle. *Am J Obstet Gynecol* **74** (3), 582-590.

Danforth D. N., Boyer P. K. & Graff S (1946) Fluctuations in weight, haematocrit and plasma protein with the menstrual cycle. *Endocrinology* **39,** 188-193.

Davidson B. J., Rea C D. & Valenzuela G J (1988) Atrial natriuretic peptide, plasma renin activity, and aldosterone in women on estrogen therapy and with premenstrual syndrome *Fertil Steril* **50** (5), 743-746.

Edwards O. M. & Bayliss R. I. S. (1973) Urinary excretion of water and electrolytes in normal females during the follicular and luteal phases of the menstrual cycle: the effect of posture. *Clin Sci Mol Med* **45,** 495-504.

Ehrlich E N (1982) The significance of increased secretion of aldosterone and deoxycorticosterone in normal pregnancy. In *Pregnancy Hypertension* (Sammour M., Symonds E M., Zuspan F. P. & El-Tomi N., eds), Ains Shams University Press, Cairo, Ch. 14, pp 113-124

Epstein M. (1978) Renal effects of head out water immersion in man Implications for an understanding of volume homeostasis *Physiol Rev* **58** (3), 529-581.

Epstein M. & Soruta T (1971) Effects of water immersion on renin-aldosterone and renal sodium handling in normal man. *J Appl Physiol* **31** (3), 368-374

Epstein M., Levinson R & Loutzenhiser R (1976) Effects of water immersion on renal haemodynamics in normal man. *J Appl Physiol* **41,** 230-233.

Golub L J., Menduke H. & Conly S S (1965) Weight changes in college women during the menstrual cycle. *Am J Obstet Gynecol* **91,** 89-94.

Goulding A. & McChesney R. (1977) Oestrogen-progestogen oral contraceptives and urinary calcium excretion. *Clin Endocrinol* **6,** 449-454

Greenhouse S. W. & Geisser S. (1959) On methods in the analysis of profile data *Psychometrika* **24** (2), 95-112.

Hassan Ahmad A K., Carter G. & Tooke J. E. (1990) Postural vasoconstriction in women during the normal menstrual cycle. *Clin Sci* **78,** 39-47

Hussain S. Y., O'Brien P. M. S , De Souza V., Okonofua F. & Dandona P. (1990) Reduced atrial natriuretic peptide concentrations in premenstrual syndrome. *Br J Obstet Gynaecol* **97,** 397-401.

Hussain S & O'Brien P. M. S (1989) Atrial natriuretic peptide in the menstrual cycle and in premenstrual syndrome. *Contemp Rev Obstet Gynaecol* **1,** 279-282

Jackson B., Hodsman G P., Allen P. S. & Johnston C. I. (1987) Plasma atrial natriuretic factor in pregnancy *Clin Exper Hypertens Pregnancy* **B6** (3): 421-429

Janowsky D. S., Berens S. C. & Davis J. M. (1973) Correlations between mood, weight and electrolytes during the menstrual cycle: A renin-angiotensin-aldosterone hypothesis of premenstrual tension. *Psychosom Med* **35** (2), 143-154.

Katz F. H. & Romfh P. (1972) Plasma aldosterone and renin activity during the menstrual cycle. *J Clin Endocrinol Metab* **34** (5), 819-821.

Landau R. L. & Lugibihl K (1958) Inhibition of the sodium retaining influence of aldosterone by progesterone. *Clin Endocrinol* **18,** 1237-1245

MacGregor G. A., Roulston J. E , Markandu N. D., Jones J. C. & Wardener H E. de. (1979) Is idiopathic oedema idiopathic? *Lancet* **i,** 397-400

Michelakis A. M., Stant E G. & Brill A. B. (1971) Sodium space and electrolyte excretion during the menstrual cycle. *Am J Obstet Gynecol* **109,** 150-154.

Michelakis A M , Yoshida H. & Dormois J. C. (1975) Plasma renin activity and plasma aldosterone during the normal menstrual cycle. *Am J Obstet Gynecol* **123,** 724-726.

Morton J. H. (1950) Premenstrual tension. *Am J Obstet Gynecol* **60,** 343-352.

Munday M. R., Brush M G. & Taylor R. W (1981) Correlations between progesterone, oestradiol and aldosterone levels in the premenstrual syndrome. *Clin Endocrinol* **14,** 1-9.

O'Brien P. M. S., Craven D., Selby C. & Symonds E. M. (1979) Treatment of premenstrual syndrome by spironolactone. *Br J Obstet Gynaecol* **86**, 146-147.

O'Brien P. M. S., Selby C. & Symonds E. M. (1980) Progesterone, fluid and electyrolytes in premenstrual syndrome. *Br Med J* **280**, 1161-3.

O'Hare J.P., Watson M., Penney M. D., Hampton D., Roland J. M. & Corrall R. J M. (1985) Urinary prostaglandin E and antidiuretic hormone during water immersion in man. *Clin Sci* **69**, 493-496.

Okey R & Stewart D. (1933) Diet and blood cholesterol in normal women. *J Biol Chem* **99**, 717

Oparil S., Ehrlich E. N. & Lindheimer M. D. (1975) Effect of progesterone on renal sodium handling in man: relation to aldosterone excretion and plasma renin activity. *Clin Sci Mol Med* **49**, 139-147.

Pitkin R. M., Reynolds W. A., Williams G. A. & Hargis G. K. (1978) Calcium-regulating hormones during the menstrual cycle. *J Clin Endocrinol Metab* **47**, 626-632.

Prowse C., George E., Micklem L. R., Hornsey V., Brow J. & James K. (1989) Human atrial natriuretic factor (ANF): Characterization of a monoclonal antibody panel and its use in radio-immunassay. *J Immunol Methods* **118**, 91-100.

Sweeney J. S. (1934) Menstrual oedema. *JAMA* **103**, 234.

Taggart N. (1962) Diet, activity and body weight A study of variations in a woman. *Br J Nutr* **16**, 223-235.

Tan A. C. I. T. L., Rosmalen F. M. A., Theeleh B. G. A., Kloppenborg P. W. C., Benraad H. B & Benraad Th. J. (1987) Atrial natriuretic peptide—the influence of various physiological and sampling conditions. *Ann Clin Biochem* **24**, 500-507.

Thomas C. B. (1953) Some observations on the relationship between weight changes following sodium restriction and those associated with the menstrual cycle in normal young women. *Ann Int Med* **39**, 289.

Thorn G. W., Nelson K. R. & Thorn D. W. (1938) A study of the mechanism of edema associated with menstruation. *Endocrinol* **22** (2), 155-163.

Watson P. E. & Robinson M. F. (1965) Variations in body-weight of young women during the menstrual cycle. *Br J Nutr* **19**, 237-248.

Watts J. F. F., Butt W. R., Logan Edwards R. & Holder G (1985) Hormonal studies in women with premenstrual tension. *Br J Obstet Gynaecol* **92**, 247-255.

Weinberger M .H., Kramer N. J., Grim C. E. & Petersen L. P. (1977) The effect of posture and saline loading on plasma renin activity and aldosterone concentration in pregnant, non-pregnant and estrogen treated women. *J Clin Endocrinol Metab* **44**, 69-77.

Young M. M., Jasani C., Smith D. A. & Nordin B. E. C. (1968) Some effects of ethinyl oestradiol on calcium and phosphorus metabolism in osteoporosis. *Clin Sci* **34**, 411-417.

Received 17 April 1991
Accepted 19 October 1991

British Journal of Obstetrics and Gynaecology
March 1992, Vol. 99, pp. 253–257

REPRODUCTIVE SCIENCE

Increased whole blood platelet aggregation in normal pregnancy can be prevented *in vitro* by aspirin and dazmegrel (UK38485)

LUCY A. NORRIS
BRIAN L. SHEPPARD
JOHN BONNAR

Department of Obstetrics and
Gynaecology
Sir Patrick Dun's Research Centre
TCD Medical School
St James's Hospital, Dublin 8

ABSTRACT

Objective To determine the effect of normal pregnancy and the early puerperium on whole blood platelet aggregation and to assess the role of thromboxane A2 (TXA2) in platelet aggregation in pregnancy.

Design A prospective descriptive study.

Setting TCD Medical School, St James's Hospital, Dublin.

Subjects Twenty healthy primigravidae who remained normotensive during pregnancy and the puerperium.

Interventions 20 ml blood samples were obtained serially at 12, 20, 28, 32 and 36 weeks gestation, during established labour and at 1 h, 24 h, 48 h and 6 weeks after delivery.

Main outcome measures Whole blood platelet aggregation in response to aggregating agents ADP, PAF (platelet aggregating factor) collagen, adrenaline and arachidonic acid (AA) at each stage of pregnancy and peuerperium was measured using a particle counting technique. The *in vitro* effect of aspirin and dazmegrel (thromboxane synthetase inhibitor UK38485) on platelet aggregation in pregnancy was also investigated.

Results Platelet aggregation in response to collagen, adrenaline, ADP and AA were increased in the last trimester, during labour and at 1 h after delivery but decreased 24–48 h after delivery. Platelet aggregation in response to AA, collagen and adrenalin was reduced by both aspirin and dazmegrel.

Conclusions The earliest and most marked increases in platelet aggregation during normal pregnancy were found in response to AA and collagen. These platelet changes were prevented when whole blood was pre-incubated with either aspirin or dazmegrel. This suggests that enhanced production of TXA2 is reponsible for increased platelet reactivity in normal pregnancy.

In normal pregnancy, extensive changes in the blood coagulation and fibrinolytic systems have been reported; however, little is known about the changes in platelet function (Stirling *et al* 1984). Pro-aggregatory thromboxane A2 (TXA2) is increased in normal pregnancy (Ylikorkala *et al* 1980) and the site of this increased biosynthesis is mainly in platelets (Fitzgerald *et al* 1987). Increased platelet aggregation has been reported in normal pregnancy using platelet rich plasma (Leuschen *et al* 1986; Andrews *et al.* 1985). Louden *et al.* (1990) studied eight women longitudinally and found that platelet aggregation increased in response to some aggregating agents, although serum TXA2 was unchanged. Red blood cells are intimately involved in the process of platelet activation (Gaardner *et al* 1961) and therefore platelet studies in whole blood will reflect *in vivo* events more accurately. We have investigated whole blood platelet aggregation in 20 women throughout normal pregnancy, labour and the puerperium. The *in vitro* effect of aspirin and the thromboxane synthetase inhibitor dazmegrel (Cross *et al.* 1986) was also investigated to assess the role of TXA2 in platelet aggregation in normal pregnancy.

Subjects and methods

Twenty healthy primigravidae, who had given full and informed consent, participated in the study. Each woman had 20 ml of blood taken at 12, 20, 28, 32, and 36 weeks gestation, during established labour and again at 1 h, 24 h, 48 h and 6 weeks after delivery. All women remained normotensive during pregnancy and the puerperium and avoided any drugs known to affect platelet function. None of them received prostaglandins for cervical ripening.

Blood collection

Venous blood was withdrawn from the antecubital vein with the minimum of venous stasis using a monovette system of

Correspondence Lucy A. Norris.

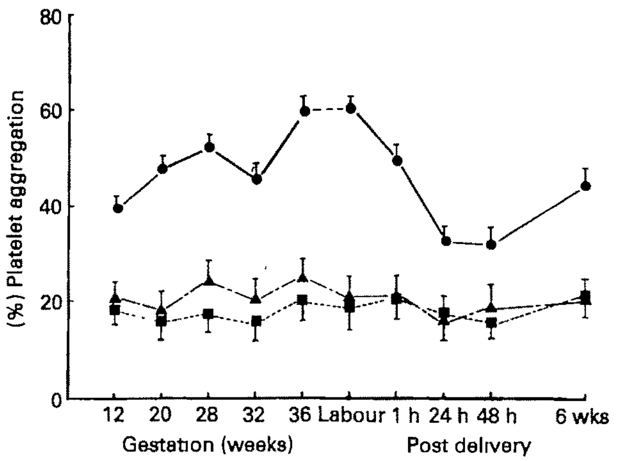


Fig. 1. Collagen (0·5 µg/ml) induced platelet aggregation (%) in whole blood samples from 20 women during normal pregnancy, labour and at 1 h, 24 h, 48 h and 6 weeks after delivery (●——●). Platelet aggregation after incubation with aspirin (100 µM) (■——■). Platelet aggregation after incubation with dazmegrel (100 µM) (▲——▲). Results shown are mean ± SEM.

blood collection. A 21 gauge needle was used due to the number of blood samples taken during labour and after delivery. Blood for whole blood platelet aggregation was collected into 3·13% sodium citrate (10% v/v) and was incubated at 37°C for 30 min.

Platelet aggregation

Platelet aggregation was measured using a modification of the method described by Fox *et al.* (1982). A series of 480 µl samples of whole blood was stirred at 1000 rpm at 37°C for 2 min; 1 ml of fixative (0·16% w/v formaldehyde, 4·6 mM disodium EDTA, 4·5 mM disodium hydrogenphosphate, 1·6 mM potassium dihydrogen phosphate, pH 7·4) was added to the first sample. 20 µl of one of the following aggregating agents was added to each tube so that their final concentrations were as follows: adenosine diphosphate (ADP) 0·5 µM, platelet-activating-factor (PAF) 0·05 µM, collagen 0·5 µg/ml, adrenaline 1·0 µM, and arachidonic acid (AA) 0·2 mM. The tubes were stirred for a further 30 s–2 min depending on the aggregating agent used.

Concentrations and incubation times of each aggregating agent were chosen as those required to produce 30–50% platelet aggregation in a series of preliminary experiments using healthy non-pregnant women.

A 1 ml solution of fixative was added and the samples were spun at 200 *g* for 1 min and read on a thrombocounter C. Platelet aggregation was expressed as the percentage fall in the number of single platelets after incubation with an aggregating agent compared with the number of platelets present before addition of the aggregating agent.

Inhibition by aspirin and dazmegrel

A 200 µl solution of aspirin or dazmegrel (to a final concentration of 100 µM for each) was added to 2·8 ml of whole blood immediately after venepuncture. This was then incubated at 37°C for 35 min as above and the procedure for platelet aggregation was repeated.

Materials

ADP, PAF, EDTA, and aspirin (acetylsalycilic acid) were supplied by the Sigma Chemical Co. St Louis, MO, USA). Collagen suspension, adrenaline bitartrate and AA were supplied by Semmelweis (Milan, Italy). Dazmegrel (UK38485) was provided by Pfizer Research (Sandwich, Kent, UK). All other chemicals were of analar grade. PAF was dissolved in absolute ethanol (stock solution) and was subsequently diluted in human serum albumin (0·25%). AA was dissolved in bovine serum albumin (100 mg/ml) and stored in the dark at −20°C. Before use all aggregating agents were diluted using saline (150 mM) and kept on ice. Dazmegrel (pH 8·5) was dissolved in NaOH (0·1 N) and was subsequently diluted with saline (150 mM).

Statistics

A normal probability plot showed that the data were normally distributed, they were therefore expressed as mean (SEM) values. The data were analysed using repeated measures one-way analysis of variance to determine pregnancy and post delivery effects and a two-way analysis of variance to examine the effects of aspirin and dazmegrel. Statistical significance for analysis of variance was taken as $P<0{\cdot}05$. Subsequent comparison between the pregnancy stages was performed using paired and unpaired Student's *t* test. Statistical significance was taken as $P<0{\cdot}01$ to allow for repeated use of individual *t* tests.

Results

Serial changes in platelet aggregation

Collagen (Fig. 1). Repeated measures analysis of variance showed that pregnancy had a highly significant effect on collagen induced platelet aggregation ($P<0{\cdot}0001$). Levels were found to increase significantly from 20 weeks gestation onwards reaching a maximum during labour compared with 6 weeks after delivery ($P<0{\cdot}001$). Platelet aggregation dropped

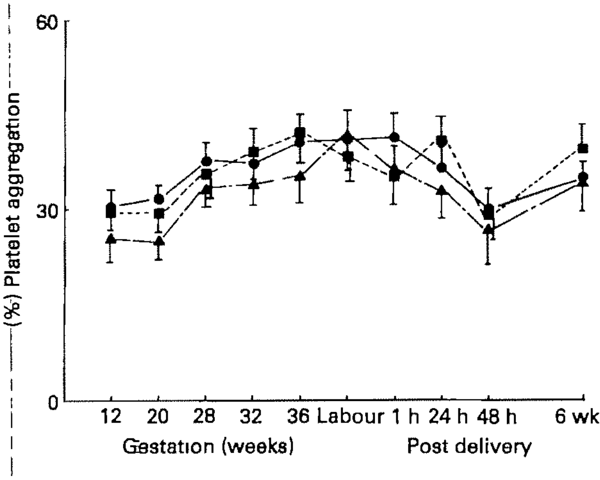


Fig. 2. Adenosine diphosphate (0·5 µm) induced platelet aggregation (%) in whole blood samples from 20 women during normal pregnancy during labour and at 1 h, 24 h, 48 h, and 6 weeks after delivery. Effects of aspirin and dazmegrel. For explanation of symbols see Fig. 1.

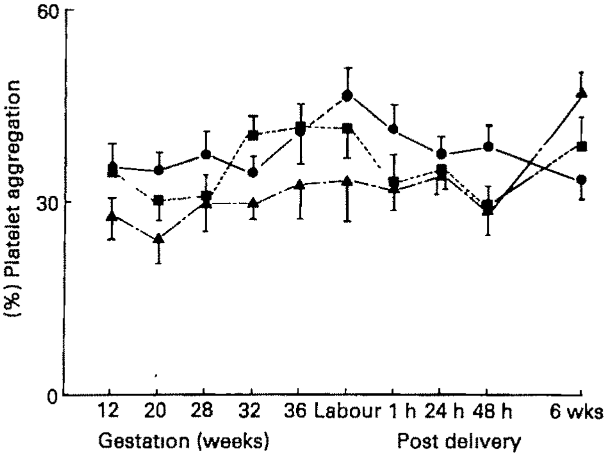


Fig. 3. Platelet aggregating factor (0·05 µM) induced platelet aggregation (%) in whole blood samples from 20 women during normal pregnancy, during labour and at 1 h, 24 h, 48 h, and 6 weeks after delivery, effects of aspirin and dazmegrel For explanation of symbols see Fig. 1

sharply 24–48 h after delivery to a level which was significantly lower than during pregnancy from 20 weeks onwards ($P<0{\cdot}001$). A slight increase was noted at 6 weeks after delivery but this was not significant

ADP (Fig. 2). ADP induced aggregation was also significantly altered by pregnancy ($P<0{\cdot}02$). a significant increase was observed at 36 weeks when compared with 12 ($P<0{\cdot}01$) and 20 weeks ($P<0{\cdot}005$). This increase was maintained during labour and at 1 h after delivery. A gradual decrease was observed 24–48 h after delivery followed by a slight increase at 6 weeks after delivery but these changes were not statistically significant.

PAF (Fig. 3). PAF induced aggregation was not significantly affected by pregnancy. A slight increase was noted during labour but this was not statistically significant when compared with either early pregnancy or post-delivery levels

AA (Fig. 4). Pregnancy had a highly significant effect on AA induced aggregation ($P<0{\cdot}02$). Levels of aggregation were significantly higher at 32 and 36 weeks ($P<0{\cdot}01$; $P<0{\cdot}001$) than at 20 weeks gestation. This increase reached a maximum during labour when it was significantly higher than at 12 and 20 weeks gestation or at 6 weeks after delivery ($P<0{\cdot}001$). A gradual decrease was observed after delivery until 48 h *post-partum* when levels of aggregation were significantly lower than at 36 weeks gestation ($P<0{\cdot}003$) and during labour ($P<0{\cdot}001$).

Adrenaline (Fig. 5). Adrenaline induced aggregation was significantly altered by pregnancy ($P<0{\cdot}03$). A gradual increase in aggregation was observed from 12 weeks onwards and at 36 weeks, levels were significantly higher than at 12 weeks gestation ($P<0{\cdot}005$). A slight decrease occurred during labour which continued after delivery. At 48 h *postpartum*, levels of aggregation were significantly lower than at 28–36 weeks gestation or during labour ($P<0{\cdot}001$). At 6 weeks *post-partum*, levels had increased slightly and were similar to those observed in the first trimester

Effects of aspirin and dazmegrel

Aspirin and dazmegrel had a highly significant effect on both collagen and AA induced aggregation in normal pregnancy ($P<0{\cdot}001$). A significant interaction was also found between the inhibitor used and the stage of pregnancy for collagen ($P<0{\cdot}05$) and AA induced aggregation ($P<0{\cdot}003$). This meant that the pregnancy related increase in collagen and AA induced aggregation was prevented when blood was treated with either aspirin or dazmegrel. Aspirin and dazmegrel also had a significant effect on adrenaline induced aggregation in normal pregnancy ($P<0{\cdot}001$), however, no significnat interaction was found between either platelet inhibitor used and stage of pregnancy. Therefore, although adrenaline induced aggregation was significantly reduced by both aspirin and dazmegrel, the pregnancy effect was not removed by either inhibitor.

Aspirin or dazmegrel did not significantly affect ADP or PAF induced aggregation in whole blood in normal pregnancy.

Discussion

Our results indicate an increased platelet reactivity in the third

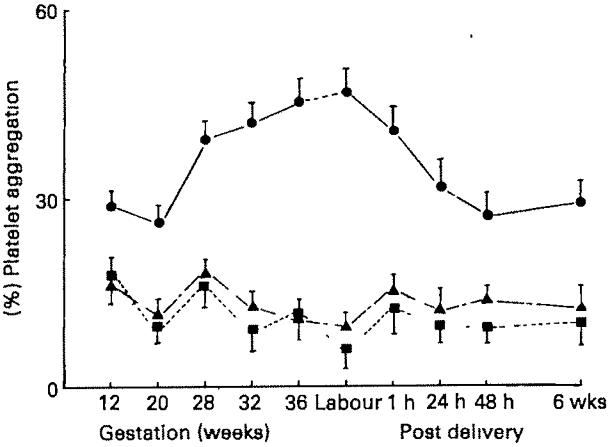


Fig. 4. Arachidonic acid (0·2 mM) induced platelet aggregation (%) in whole blood samples from 20 women during normal pregnancy, during labour and at 1 h, 24 h, 48 h, and 6 weeks after delivery; effects of aspirin and dazmegrel. For explanation of symbols see Fig. 1.

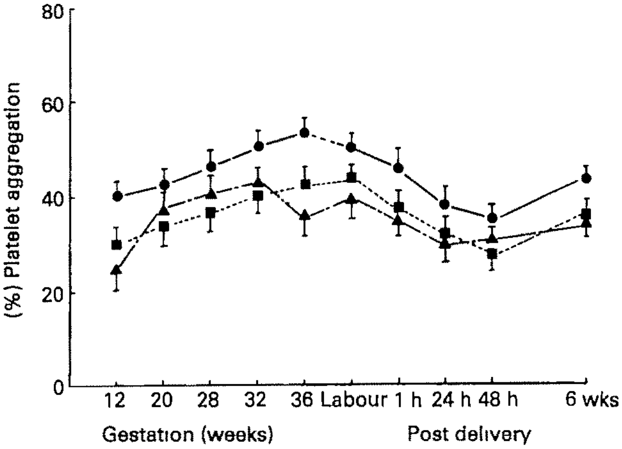


Fig. 5. Adrenaline (1·0 µM) induced platelet aggregation (%) in whole blood samples from 20 women during normal pregnancy, during labour and at 1 h, 24 h, 48 h, and 6 weeks after delivery; effects of aspirin and dazmegrel. For explanation of symbols see Fig. 1

trimester of normal pregnancy particularly in response to collagen and AA which disappears within 24–48 h of delivery. Increased platelet aggregation has been reported with a variety of aggregating agents (Andrews *et al.* 1985; Lewis *et al* 1980; Hoche *et al.* 1983). Leuschen *et al.* (1986), using an impedance method and concentrations of aggregating agents at least 10 times greater than those used in the present study, found similar increases in whole blood platelet aggregation at 25 and 31 weeks gestation when compared with 4–6 weeks *postpartum*. In a longitudinal study of eight patients, Louden *et al.* (1990) found an increased whole blood platelet response to AA and adrenaline in the third trimester of normal pregnancy. Using platelet-rich plasma, O'Brien *et al.* (1986) found platelet aggregation to be decreased in normal pregnant women compared with non pregnant controls. Morrison *et al.* (1985) found that lower concentrations of AA were required to induce maximal platelet ^{14}C-labelled serotonin release in normal pregnant women than at 6 weeks after their delivery. This suggested an increased platelet sensitivity to AA which occurred as early as 16 weeks gestation.

Platelet aggregation has been reported to increase in the follicular phase of the menstrual cycle (Yamazaki *et al* 1979) and also in women taking oestrogen containing oral contraceptives (McGrath *et al.* 1975; Norris *et al.* 1988), suggesting a possible relation between oestrogen levels and platelet aggregation. Since oestrogen levels are known to increase during normal pregnancy, this may explain the increased platelet aggregation found in our study. The rapid decrease in platelet reactivity following delivery could be explained by the decrease in oestrogen levels or a placental effect.

Our results showed that platelet aggregation in response to all of the aggregating agents studied was increased signficantly during labour and at 1 h after delivery. Noort *et al.* (1990) found an increase in TXA2 excretion in advanced labour compared with late pregnancy. Plasma TXA2 was also found to be increased at delivery (Suarez *et al.* 1988). The enhanced platelet reactivity during labour and at 1 h after delivery may therefore be related to increased platelet production of TXA2.

During the early puerperium, a decrease in platelet aggregation was observed. The platelet population at this stage may contain a large proportion of exhausted platelets which have already undergone aggregation and release at delivery and may be unresponsive to aggregating agents. As these platelets are replaced by younger and more responsive platelets then a gradual increase in platelet aggregation occurs.

The most marked changes in this study of platelet aggregation were in response to collagen and AA. Platelet activation in response to both these agents depends to a large extent on the synthesis of TXA2. The increases in platelet activation in response to collagen and AA were prevented when the blood was incubated with aspirin, which inhibits the cyclo-oxygenase enzyme, or dazmegrel, which inhibits the thromboxane synthetase enzyme.

When platelet cyclo-oxygenase is inhibited, conversion of arachidonic acid to TXA2 and also to prostaglandins PGD_2 and PGI_2 is prevented, when thromboxane synthetase is inhibited, only production of TXA2 is prevented and an increased compensatory production of PGI_2 and PGE_2 may occur (Defryn *et al.* 1982; Parry *et al.* 1982).

Our results suggest that since dazmegrel, a potent inhibitor of thromboxane synthetase, successfully inhibited the increased platelet aggregation observed, that TXA2 rather than the other products of the cyclo-oxygenase pathway is directly responsible for the increased platelet aggregation seen in normal pregnancy. This may be achieved by increased availability of the substrate for TXA2 production, AA, or by an activation of the thromboxane synthetase enzyme itself. Alternatively an increase in platelet TXA2 receptor sensitivity may be responsible.

Our findings are consistent with the increased serum and plasma levels of TXA2 found by several authors (Mitchell *et al.* 1978; Ylikorkala *et al.* 1980; Greer *et al.* 1988) and also with the findings of Fitzgerald *et al.* (1987) who observed that increased urinary metabolites of TXA2 in normal pregnancy were mainly of platelet origin. However, Louden *et al.* (1990) and Koullapis *et al.* (1982) found serum and plasma TXA2 levels to be unchanged.

During normal pregnancy extensive vascular changes take place, particularly in the uterus where blood flow to the placenta increases gradually from 50 ml/min in early pregnancy to 800 ml/min at delivery (Bonnar 1987). During childbirth, when placental separation occurs, the large blood flow to the placenta must be staunched in seconds. This is achieved by a combination of myometrial vascular compression, platelet and coagulation activation, leading to thrombotic occlusion of the uteroplacental vessels. The enhanced responsiveness of platelets observed during late pregnancy and labour would facilitate this haemostatic process.

Inhibitors of TXA2 production such as aspirin have been shown to be successful in reducing the occurrence of pre-eclampsia in high risk patients (Wallenburg *et al.* 1986). This would support a possible role for enhanced TXA2 induced platelet activation in pre-eclampsia.

In conclusion our results show that normal pregnancy is accompanied by increased whole blood platelet aggregation particularly in response to collagen and arachidonic acid. This increased aggregation was prevented when the blood was incubated with either aspirin or dazmegrel indicating that enhanced production of TXA2 may be responsible for the increased aggregation seen in normal pregnancy.

Acknowledgments

This study was funded by a Wellcome Trust research grant. Pfizer Research, Sandwich, Kent, UK, kindly supplied the dazmegrel.

References

Andrews N. P., Broughton-Pipkin F. & Heptinstall S. (1985) Blood platelet behaviour in mothers and neonates. *Thromb Haemost* **53**, 428–432.

Bonnar J. (1987) Haemostasis and coagulation disorders in pregnancy. In *Thrombosis and Haemostasis* (Bloom A. L. & Thomas B. P., eds.) Churchill Livingston, p. 570.

Cross P. E., Dickinson R. P., Parry M. J & Randall M. J. (1986) Selective thromboxane synthetase inhibitors. 2. 3-(1H-imidazol-1-ylmethyl)-2-methyl-1H-indole-1-propanoic acid and analogues. *J Med Chem* **29**, 342-346.

Defryn G., Deckmyn H. & Vermylen J. (1982) A thromboxane synthetase re-orientates endoperoxide metabolism in whole blood towards prostacyclin and PGE_2. *Thromb Res* **26**, 389–400.

Fitzgerald D. J , Mayo G., Catella F, Entmann S. S. & Fitzgerald G. A. (1987) Increased thromboxane biosynthesis in normal pregnancy is mainly derived from platelets. *Am J Obstet Gynecol* **157,** 325–330.

Fox S. C., Burgess-Wilson M., Heptinstall S. & Mitchell J. R. A. (1982) Platelet aggregation in whole blood determined using the Ultra-flo 100 platelet counter. *Thromb Haemost* **48,** 327–329.

Gaardner A., Jonsen J , Laland S., Hellem A. & Owren P. A. (1961) ADP in red cells as a factor in the adhesiveness of human blood platelets. *Nature* **192,** 531–532.

Greer I. A., Walker J. J. & Lunan C. B. (1988) Increased platelet reactivity in pregnancy induced hypertension and uncomplicated diabetic pregnancy: an indication for anti-platelet therapy? *Br J Obstet Gynaecol* **95,** 1204–1206.

Hoche C., Kefalides A., Dadak C. & Sinzinger H (1983) Platelet sensitivity to prostacyclin in pregnancy and the puerperium In *Prostacyclin in Pregnancy.* (Lewis, P.J., ed.) Raven Press, New York, pp. 189–193

Koullapis E. N., Nicolaides K. H., Collins W. P., Rodeck C. H. & Cambell S. (1982) Plasma prostanoids in pregnancy induced hypertension. *Br J Obstet Gynaecol* **89,** 617–621

Leuschen M. P., Davis R. B , Boyd D. & Goodlin R. C. (1986) Comparative evaluation of antepartum and post partum platelet activation in smokers and non-smokers. *Am J Obstet Gynecol* **155,** 1276–1280.

Lewis P. J., Boylan P., Friedman L A., Hensbey C. N. & Downing I. (1980) Prostacyclin in pregnancy. *Br Med J* **282,** 1581–1582.

Louden K. A., Broughton-Pipkin F., Heptinstall S., Fox S. C., Mitchell J. R. A. & Symonds E. M. (1990) A longitudinal study of platelet behaviour and thromboxane production in whole blood in normal pregnancy and the puerperium. *Br J Obstet Gynaecol* **97,** 1108–1114

McGrath K. M. & Castaldi P A. (1975) Changes in coagulation factors and platelet function in response to progestational agents. *Haemostasis* **4,** 65–72.

Mitchell M D., Bibby J. G , Hicks B. R., Redman C. W. G., Anderson A. B. & Turnbull A. C (1978) Thromboxane A_2 and human parturition: concentration in the plasma and production *in vitro. J Endocrinol* **78,** 435–441

Morrison R , Crawford J., MacPherson M. & Heptinstall S (1985) Platelet behaviour in normal pregnancy, pregnancy complicated by essential hypertension and pregnancy-induced hypertension. *Thromb Haemost* **54,** 607–611

Noort W A. & Keirse MJ (1990) Prostacyclin and thromboxane metabolites changes in pregnancy and labour *Eur J Obstet Gynecol Reprod Biol* **35,** (1) 15–21.

Norris L. A , Carroll M. E. & Bonnar J. (1988) Effect of triphasic oral contraceptives on whole blood platelet aggregation. *Irish Journal of Medical Science* **157,** 357.

O'Brien W F, Saba H. I., Knuppel R. A., Scerbo J. C. & Cohen G R. (1986) Alterations in platelet concentration and aggregation in normal pregnancy and pre-eclampsia. *Am J Obstet Gynecol* **155,** 466–490.

Parry M. J., Randall M. J., Hawkeswood E., Cross P E. & Dickinson R. P. (1982) Enhanced production of prostacyclin in blood after treatment with selective thromboxane synthetase inhibitor UK-38485. *Br J Pharmacol* **77,** 547P

Stirling Y., Woolf L. North W. R. S., Seghatchian M. J. & Meade T. W. (1984) Haemostasis in normal pregnancy. *Thromb Haemost* **52,** 176–182.

Suarez C. R., Gonzales J., Menendez Fareed J , Fresco R. & Walenga J. (1988) Neonatal and maternal platelets. activation at time of birth. *Am J Haem* **29,** 18–21.

Wallenburg H. C S., Makovitz J. W. , Dekker G. A. & Rotmans N (1986) Low dose aspirin prevents pregnancy-induced-hypertension and pre-eclampsia in angiotensin sensitive primigravidae. *Lancet* **i,** 1–3.

Yamazaki H., Motomiya T., Kikutani N., Sakakibara C., Watanabe S , Numata M. & Noguchi K. (1979) Platelet aggregation during the menstrual cycle and pregnancy. *Thromb Res* **14,** 333–340.

Ylikorkala O. & Viinikka L. (1980) Thromboxane A2 in pregnancy and puerperium *Br Med J* **281,** 1601–1602.

Received 15 April 1991
Accepted 10 October 1991

British Journal of Obstetrics and Gynaecology
March 1992, Vol. 99, pp. 258–264

CASE REPORTS

Multiple fetal anomalies in the first trimester; detection using transvaginal ultrasound and therapeutic abortion using mifepristone (RU486) in conjunction with gemeprost vaginal pessaries

R. C. HENSHAW
Clinical Research Fellow
A. P. M. SMITH
Staff Doctor
N. C. SMITH
Consultant

Department of Obstetrics and Gynaecology, Aberdeen Maternity Hospital, Cornhill Road, Aberdeen AB9 2ZD

G. I. MURRAY
Lecturer

Department of Pathology, University of Aberdeen, Polwarth Building, Foresterhill, Aberdeen AB9 2ZD

Case report

A 30-year-old woman booked for antenatal care at 10 weeks gestation in her second pregnancy. Her previous pregnancy had been uncomplicated, and had resulted in the birth of a healthy female infant. An ultrasound scan was performed to confirm gestation, but there was difficulty in obtaining a satisfactory crown-rump measurement using the transabdominal probe. To obtain better resolution, a transvaginal ultrasound scan was performed using a 7·5 MHz mechanical sector probe. Fetal heart movements were seen but the fetal head was clearly abnormal, and there was a large defect in the lower lumbar region of the fetal spine (Fig. 1). Although the appearances suggested anencephaly with spina bifida, the presence of multiple anomalies raised the possibility that the fetus was affected by an associated syndrome.

The woman was informed of the detected defects and of the poor prognosis for the pregnancy. She decided to opt for pregnancy termination. It was decided an attempt would be made to obtain the fetus intact, utilizing mifepristone in conjunction with gemeprost vaginal pessaries, to allow pathological confirmation of the ultrasound diagnosis. Written informed consent was given for this procedure.

The woman attended hospital a few days later, when 600 mg mifepristone was administered orally. She returned home and 48 h later she was admitted to the hospital gynaecological day case ward. Gemeprost 1 mg vaginal pessaries were administered every 3 h; a total of three pessaries were used. The products of conception were expelled 8 h after the first pessary was inserted, and abortion appeared to be complete. The woman was discharged home later the same day. The intact fetus were sent for pathological and karyotype analysis.

The woman was reviewed 2 weeks later. Vaginal bleeding had ceased and pelvic examination was normal; a diagnosis of complete abortion was made. Haemoglobin was 14·1 g/dl before the procedure and 14·4 g/dl at the follow-up visit.

Pathological examination confirmed an 11-week fetus with a major neural tube defect (anencephaly and spina bifida) and exomphalos. There was no polydactyly or evidence of renal cysts to suggest Meckel-Gruber syndrome or other genetic disorders. Chromosome analysis was not possible as skin fibroblasts failed to grow in culture.

Discussion

The diagnosis of fetal anomalies using transvaginal ultra-

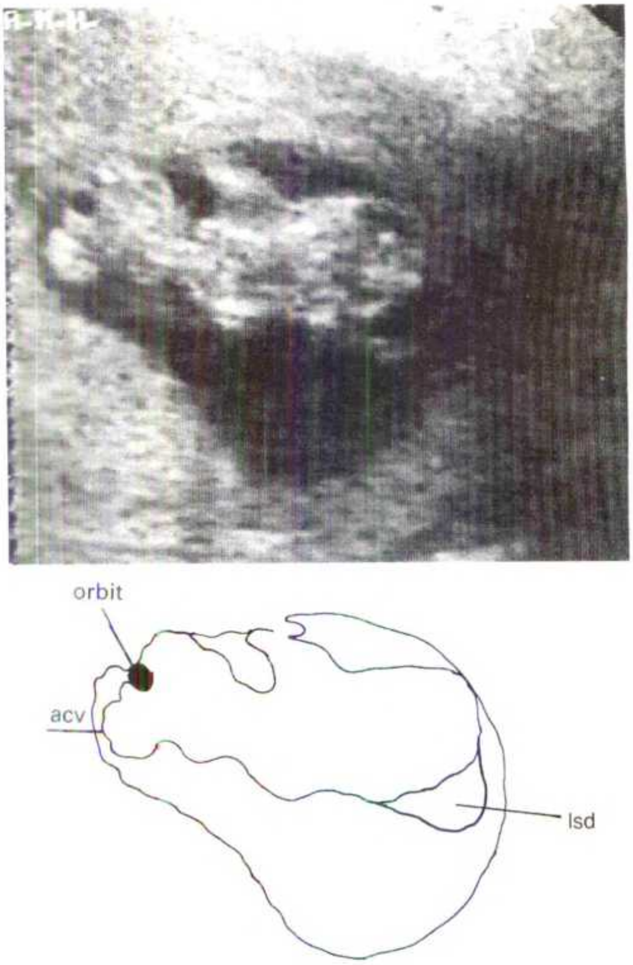


Fig. 1. An ultrasonogram at 10 weeks gestation showing an absent cranial vault (acv) and lumbosacral spinal defect (lsd).

Correspondence: Dr R. C. Henshaw.

sonography has already been described (Cullen *et al.* 1990). The fetus is more clearly imaged because of the combined proximity of the probe to the fetus and the consequent ability to utilize higher frequency.

In the past, the management of fetal anomalies diagnosed in the first trimester of pregnancy has been surgical vacuum aspiration under general anaesthesia. However, this destructive procedure does not allow full pathological examination of the fetus to confirm the diagnosis. This is clearly of importance when multiple fetal anomalies have been seen which may form part of an inherited syndrome (in our patient Meckel-Gruber syndrome, an autosomal recessive disorder, was suspected); identification of such syndromes may influence the management of any future pregnancies, and this is important when counselling for risk of occurrence.

Mifepristone (RU486-Mifegyne), in conjunction with gemeprost vaginal pessaries, has been used in both early first trimester and second trimester pregnancy termination with a high degree of success (Roger & Baird 1990; UK Multicentre Trial 1990). In our patient abortion was achieved late in the first trimester utilizing a similar regimen. The procedure can be performed as a day case and has the great advantage of providing an intact specimen for pathological examination. This is the first description of mifepristone use in the first trimester for the induced abortion of a congenitally abnormal fetus.

References

Cullen M. T, Green J., Whetham J, Salafia C., Gabrieth S. & Hobbins J. (1990) Transvaginal ultrasonic detection of congenital anomalies in the first trimester. *Am J Obstet Gynecol* **163**, 466–476

Roger M. W & Baird D. T. (1990) Pretreatment with mifepristone (RU486) reduces interval between prostaglandin administration and expulsion in second trimester abortion. *Br J Obstet Gynaecol* **97**, 41–45.

UK Multicentre Trial (1990) The efficacy and tolerance of mifepristone and prostaglandin in first trimester termination of pregnancy. *Br J Obstet Gynaecol* **97**, 480–486

Received 3 September 1991
Accepted 15 October 1991

British Journal of Obstretrics and Gynaecology
March 1992, Vol. 99, pp. 259–260

Pregnancy following intravaginal embryo transportation

J. DIANE CRITCHLOW
Clinical Scientist

PHILLIP L. MATSON
Consultant Clinical Scientist

Regional IVF Unit, Saint Mary's Hospital,
Whitworth Park, Manchester M13 0JH

STEPHEN KILLICK
Consultant Obstetrician/Gynaecologist

Withington Hospital, Withington, Manchester M20 8LE

BRIAN A. LIEBERMAN
Consultant Obstetrician/Gynaecologist

Regional IVF Unit, Saint Mary's Hospital,
Whitworth Park, Manchester M13 0JH

Case report

A 35-year-old woman with secondary unexplained infertility underwent gamete intrafallopian transfer (GIFT) in September 1989 at Withington Hospital, Manchester, where in-vitro fertilization (IVF) and cryopreservation facilities were not available at that time. At laparoscopy, nine pre-ovulatory oocytes were recovered and the three oocytes judged to be the most mature were placed into the fallopian tubes, together with sperm from the partner (100 000 normal motile sperm/tube) prepared previously using a swim-up technique.

Within 30 min of the GIFT procedure, the six remaining oocytes were placed into sterile polypropylene cryotubes (3 oocytes/tube; Nunc, Gibco Europe Ltd.) containing human tubal fluid medium supplemented with HEPES buffer and 10% maternal heat-inactivated serum (Critchlow *et al.* 1990). To each of the tubes 100 000 of the prepared sperm was added. The sealed tubes in protective plastic envelopes were then positioned in the maternal vagina and held in place using a contraceptive diaphragm in the manner described by Ranoux *et al.* (1988).

The following day, the patient travelled approximately 4 miles to the Regional IVF Unit, Saint Mary's Hospital, Manchester, where the vaginal tubes were removed and the contents inspected. Three of these six oocytes showed evidence of fertilization and were cryopreserved at the pronucleate stage using the cryoprotective agent 1,2-propanediol (Troup *et al* 1990).

The patient failed to conceive following the GIFT procedure. The thawing of the cryopreserved pronucleate oocytes in August 1990 was undertaken in a replacement cycle involving pituitary suppression, using a single subcutaneous injection of goserelin 3·6 mg (Zoladex). This was administered 7 days before the expected date of the patient's menstrual period. Following menstruation, hormone replacement therapy (HRT) was started using oestradiol valerate (Progynova) 1 mg/day on days 1 to 5, 2 mg/day on days 6 to 9 and 6 mg/day thereafter, together with progesterone (Cyclogest) 200 mg on day 15, 400 mg on day 16 and 800 mg/day onwards.

On the 16th day of oestrogen therapy, all three pronucleate oocytes were thawed at the IVF unit. All of the oocytes cleaved to the 4 cell stage after overnight culture, and were replaced into the uterine cavity and the HRT continued. A urinary β-hCG pregnancy test on the 17th day after embryo replacement was positive. An ultrasound scan 6 weeks after embryo replacement demonstrated a single fetus, the pregnancy con-

Correspondence. J. Diane Critchlow

tinued and the woman was delivered vaginally of a normal female infant weighing 3·15 kg after 38 weeks gestation.

Comment

GIFT can be easily and economically introduced into hospitals, and has therefore become widely available in Units unable to offer IVF or cryopreservation facilities (Interim Licensing Authority 1991). However, the number of oocytes transferred back to the patient should be limited to a maximum of three (Interim Licensing Authority 1991) to reduce the risk of multiple pregnancy after GIFT. The use of the IVC (intravaginal culture) technique to transfer supernumerary oocytes and sperm to a local IVF unit with the facilities for cryopreservation provides a simple and cost-effective method for maximizing the chance of achieving a pregnancy per surgical procedure. This has important implications in the structuring of infertility services, both within the National Health Service and the private sector. The present report describes the first viable pregnancy achieved following the intra-vaginal transport of embryos from a GIFT unit to an IVF unit for cryopreservation.

The modified IVC protocol used in the present study in which the transported supernumerary oocytes were examined for evidence of fertilization 20–24 h after insemination, enables screening for polyspermy. In addition, cryopreservation at the 1 cell pronucleate stage offers improved embryo survival rates compared with cryopreservation at early cleavage stages (Troup *et al.* 1990). This differs from the original method of IVC (Ranoux *et al.* 1988) which involved the culture of embryos for 2 days before they were checked.

Whilst it is unlikely that every GIFT unit will be able to provide a cryopreservation service, the present report of a viable pregnancy shows it is possible for IVF centres to provide embryo storage facilities for the GIFT units within their region, with the IVC technique providing a convenient method for transport and culture of oocytes between the two units.

Acknowledgments

The authors wish to thank Mr S. A. Troup, Miss L. Brownlie, Mr G. Horne for their assistance in the laboratory and Dr R. Stevenson for management of the frozen embryo replacement cycle.

References

Critchlow J. D., Matson P. L., Troup S. A., Ibrahim Z. H. Z., Burslem R. W., Buck P. & Lieberman B. A. (1990) Fertilization in vitro of supernumerary oocytes following gamete intra-Fallopian transfer (GIFT). *Hum Reprod* **5**, 853-856.

Interim Licensing Authority for Human in-vitro Fertilization and Embryology (1991) *Sixth Report.*

Ranoux C., Aubriot F. X., Dubuisson J. B., Cardone V., Poirot C. & Chevallier O. (1988) A new in vitro fertilization technique: intravaginal culture. *Fertil Steril* **49**, 654-657.

Troup S. A., Matson P. L., Critchlow J. D., Morroll D. R., Lieberman B. A. & Burslem R. W. (1990) Cryopreservation of human embryos at the pronucleate, early cleavage, or expanded blastocyst stages. *Eur J Obstet Gynecol Reprod Biol* **38**, 133-139.

Received 21 August 1991
Accepted 24 October 1991

British Journal of Obstretrics and Gynaecology
March 1992, Vol. 99, pp. 260–262

High-dose immunoglobulin in the antenatal treatment of neonatal alloimmune thrombocytopenia: case report and review

KLAUS MARZUSCH
Department of Obstetrics and Gynaecology

MARTINA SCHNAIDT
Department of Anaesthetics and Transfusion Medicine

JOHANNES DIETL
Department of Obstetrics and Gynaecology

ELFRIEDE WIEST
Department of Obstetrics and Gynaecology

CORNELIA HOFSTAETTER
Department of Obstetrics and Gynaecology

RANGMAR GÖLZ
Department of Paediatrics, University of Tuebingen, FRG

Correspondence: K. Marzusch, Department of Obstetrics and Gynaecology, University of Tuebingen, Schleichstrasse 4, 7400 Tuebingen, FRG.

Case report

The patient was a 28-year-old woman who had first become pregnant at the age of 20. This pregnancy was terminated for psychosocial reasons. A subsequent pregnancy one year later ended in miscarriage at 9 weeks gestation and a third pregnancy, another year later, was terminated because of fetal death at 16 weeks gestation. In her next pregnancy at the age of 23, fetal hydrocephalus was detected by ultrasound at 32 weeks gestation. Subsequent ultrasound investigations showed that this was due to an intracranial haemorrhage and, for this reason, she was delivered by caesarean section at 35 weeks gestation. The 2·5 kg female infant was found to be severely thrombocytopenic (13×10^9/l) and has shown signs of profound neurological damage during her further development.

Platelet serology revealed that the mother's platelets were Zw^a (PL^{A1}) negative, the infant's were Zw^a (PL^{A1}) positive and that the maternal serum contained specific anti-Zw^a (PL^{A1}) antibodies, so that a diagnosis of neonatal alloimmune thrombocytopenia (NAT) was made. The mother had the following

HLA type: A2, A29, B8, B44, Bw4, Bw6, Cw5, Cw7, DR3, DR7, DRw52, DRw53, DQw2. She presented to us again five years later at 10 weeks gestation. Platelet serology revealed that her partner's platelet type was homozygous Zw^a/Zw^a (PL^{A1}/PL^{A1}). Her serum anti-Zw^a (PL^{A1}) titre was 1:128 in the PAIFT. The antibody specificity was confirmed in the MAIPA. No HLA-specific antibodies were detected in her serum. The patient was treated with high-dose intravenous immunoglobulin (IVIG; Sandoglobulin, Sandoz Pharmaceuticals), 1 g/kg of body weight, infused over 5 h, once a week, from the 17th to the 34th week of pregnancy. She experienced no adverse effects during IVIG treatment, and there was no significant change in the anti-Zw^a (PL^{A1}) titre in her serum. Maternal platelet counts remained constant at a mean value of $185 \times 10^9/l$. The maternal serum IgG level increased from 6·2 g/l initially to a mean value of 16·1 g/l (specimens being drawn before IVIG infusion). Fetal blood sampling by cordocentesis using a 20-guage needle guided by ultrasound at 23 weeks gestation revealed a platelet count of $40 \times 10^9/l$. The cord blood IgG level was 5·0 ng/l; no anti-Zw^a (PL^{A1}) antibody was found in cord serum with the PAIFT. After a failed attempt to puncture the umbilical cord at 34 weeks gestation, a caesarean section was performed and a 2·0 kg female infant was born. The cord blood platelet count was $20 \times 10^9/l$ and the cord serum IgG level 10·1 g/l. Again, no specific anti-Zw^a (PL^{A1}) antibody could be identified in cord serum, but large amounts of platelet-associated IgG (PAIgG) were demonstrated on the infant's platelets with the PAIFT. Zw^a (PL^{A1})-negative donor platelets were transfused on the first two days of life, resulting in good immediate increases in the platelet count. Ultrasound examinations have shown no evidence of intracranial haemorrhage and the child has developed normally in the eight months since birth.

Laboratory methods

Maternal and fetal platelet counts were determined in blood anticoagulated with ethylene-diamine-tetraacetic acid (EDTA), using a Coulter counter of the T series, and these were verified by examination of the peripheral blood smear. Blood samples obtained by cordocentesis were identified as fetal with the Kleihauer-Betke test. Maternal serum IgG levels were determined by nephelometry, and those in the cordocentesis samples by radial immunodiffusion with Partigen plates (Behringwerke, Marburg, FRG). Platelet typing and antibody specification were performed with the platelet adhesion immunofluorescence test (PAIFT) (Schneider *et al.* 1981) and with a platelet glycoprotein-specific enzyme-linked immunosorbent assay (MAIPA) (Kiefel *et al.* 1987). Maternal Zw^a (PL^{A1}) antibody titres were assessed with the PAIFT. HLA typing and screening of maternal sera for HLA antibodies were performed with the lymphocytotoxicity assay (Terasaki *et al.* 1964).

Discussion

Neonatal alloimmune thrombocytopenia is a rare disorder that often results in intracranial haemorrhage, sometimes *in utero*. The pathogenesis of NAT is similar to that of erythroblastosis fetalis. It occurs as a consequence of maternal immunization to an antigen carried by the platelets of the fetus. The maternal alloantibodies cross the placenta and lead to accelerated destruction of fetal platelets in the reticuloendothelial system.

A first-born is affected in approximately 50% of the cases (Mueller-Eckhardt *et al.* 1989), making NAT a disorder whose natural history is quite different to that of haemolytic disease of the newborn due to Rh incompatibility. The most common cause of NAT is fetomaternal incompatibility for the platelet Zw^a (PL^{A1}) antigen (Mueller-Eckhardt *et al.* 1989). In this situation, the Zw^a (PL^{A1})-negative mother bears a Zw^a (PL^{A1})-negative child, which triggers maternal production of Zw^a (PL^{A1}) antibodies.

In a prospective study of 6738 newborn infants, Blanchette *et al.* (1988) noted the incidence of NAT in Caucasians to be between 1 per 2000 and 1 per 3000 live fetuses. Neurological abnormalities occur in about 25% (Muller 1987; Reznikoff-Etievant 1988). Intracranial haemorrhages have been detected in about 10% of affected infants by sonography *in utero* (Reznikoff-Etievant 1988; Deaver *et al.* 1986). When a woman has an infant with NAT, about 75% of the subsequent children are also affected (Shulmann *et al.* 1982). Fetomaternal incompatibility for the platelet-specific antigen Zw^a (PL^{A1}) is responsible for most of the serologically proven cases of NAT in Caucasians (Mueller-Eckhardt *et al.* 1989). Mueller-Eckhardt *et al.* (1985) found anti-Zw^a (PL^{A1}) alloantibodies in two of 1211 women during pregnancy, and this finding was corroborated in a recent Danish study (Taaning *et al.* 1990). Therefore, the frequency of maternal anti-Zw^a (PL^{A1}) during pregnancy seems to be higher than that of clinically overt NAT. A possible explanation for this is that in some cases the maternal Zw^a (PL^{A1}) antibodies may not be strong enough to induce NAT, so that the disorder remains subclinical (Taaning *et al.* 1990). From the Zw^a (PL^{A1}) antigen frequency of 97·5% in Caucasians, one could expect about 1 in 50 pregnancies to be affected by Zw^a (PL^{A1}) antigen incompatibility. The more frequent development of Zw^a (PL^{A1}) antibodies in association with a certain maternal HLA-phenotype seems to be one reason for the much lower incidence of NAT: studies have shown that a woman possessing the DR3 antigen is 76·5 times more likely to form anti-Zw^a (PL^{A1}) antibodies than a woman who is DR3-negative (Muller 1987). In our case, maternal HLA typing revealed the HLA antigen DR3 in association with a high titre of anti-Zw^a (PL^{A1}) antibody. Compared with a reference range recently published (Hof *et al.* 1990), the fetal platelet count at 23 weeks gestation was low ($40 \times 10^9/l$) in our patient but was considered sufficient, and high-dose IVIG therapy was continued according to the protocol. In addition, our maternal and fetal serum IgG values during IVIG therapy were comparable with the levels in the seven pregnancies treated successfully by Bussel *et al.* (1988). No circulating anti-Zw^a (PL^{A1}) was detected in the infant's serum at 23 or 34 weeks gestation, which may have been due to binding of antibody by the fetal platelets. The infant's platelets were found to be loaded with PAIgG at 34 weeks, suggesting membrane-bound antibody. It is also possible that this PAIgG derived from the intact IgG administered during IVIG treatment, since platelets can bind antibody nonspecifically through their Fc receptors (Karas *et al.* 1982). Unfortunately, elution and identification of the bound PAIgG was not possible due to low platelet numbers.

The mechanisms involved in improving platelet counts with IVIG in some immune thrombocytopenias remain unclear according to an extensive recent review (Boshkov *et al.* 1989). Fc-receptor blockade in the reticuloendothelial system has been postulated in cases of idiopathic thrombocytopenic purpura (Fehr *et al.* 1982). In our patient one might speculate that the lack of detectable circulating anti-Zw^a (PL^{A1}) in fetal serum was due to placental blockade by exogenous IgG, but at 23 and 34 weeks gestation the infant was thrombocytopenic and platelet-bound PAIgG was detected on fetal platelets at birth. One reason for the failure of the high-dose IVIG to elevate the fetal platelet count might be that the antibody involved was complement-fixing, making Fc-receptor blockade inadequate for the prevention of platelet destruction. For this reason and for the possible implications for the outcome of IVIG therapy, it would be of interest in future cases to test whether the maternal antibody involved is complement-fixing, for example, by the method described by Heinrich *et al.* (1971). Despite very low platelet counts at birth, no evidence of intracranial haemorrhage was detected by ultrasound examination, and the child has developed normally in the eight months since birth. Since our patient was treated, two other cases have been reported that suggest that high-dose IVIG given during pregnancy in NAT does not always increase fetal platelet counts (Nicolini *et al.* 1990; Mir *et al.* 1988). This is in contrast to the successful treatment of seven pregnancies by Bussel *et al.* (1988). The treatment of choice for NAT due to Zw^a (PL^{A1}) antibodies is the repeated intrauterine transfusion of Zw^a (PL^{A1})-negative platelets to prevent intracranial haemorrhage, especially in the last trimester of pregnancy (Murphy *et al.* 1990; Nicolini *et al.* 1990). However, intrauterine transfusion of platelets guided by ultrasound requires skills that are not available at all centres. Furthermore, few blood banks are able to perform platelet serology and thus provide matched platelets for transfusion. We consider that the more conservative approach in treating NAT with exogenous immunoglobulins should not be abandoned before further studies of this treatment have been performed. In addition, intracranial haemorrhage caused by Zw^a (PL^{A1}) incompatibility may occur at the end of the first trimester (Giovangrandi *et al.* 1990), which makes treatment necessary at a stage where intrauterine platelet transfusion is not possible. Fetal blood sampling by cordocentesis should be performed as early as possible in NAT and repeated at 2–4 week intervals during IVIG therapy to assess the effectiveness of treatment. *In utero* platelet transfusions should be considered in pregnancies where the fetal platelet count is inadequate.

Acknowledgments

We gratefully acknowledge the technical assistance of Herbert Klement and Mona Dreher.

References

Blanchette V. S., Peters M. A. & Pegg-Feige K. (1988) Alloimmune thrombocytopenia. *Curr Stud Hematol Blood Transfus* **55,** 87–96.

Boshkov L. K. & Kelton J. G. (1989) Use of intravenous gamma globulin as an immune replacement and an immune suppressant. *Transfus Med Rev* **3,** 82–120.

Bussel J. B., Berkowitz R. L., McFarland J. G., Lynch L. & Chitkara U. (1988) Antenatal treatment of neonatal alloimmune thrombocytopenia. *N Engl J Med* **319,** 1374–1378.

Deaver J. E., Leppert P. C. & Zaroulis C. G. (1986) Neonatal alloimmune thrombocytopenic purpura. *Am J Perinatol* **3,** 127–131.

Fehr J., Hofmann V. & Kappeler U. (1982) Transient reversal of thrombocytopenia in idiopathic thrombocytopenic purpura by high-dose intravenous gamma globulin. *N Engl J Med* **306,** 1254–1258.

Giovangrandi Y., Daffos F., Kaplan C., Forestier F., MacAleese F. & Moirot M. (1990) Very early intracranial haemorrhage in alloimmune fetal thrombocytopenia. *Lancet* **ii,** 310.

Heinrich D. & Mueller-Eckhardt C. (1971) Micro complement fixation with platelets. A methodological analysis. *Vox Sang* **21,** 251–260.

Hof M. C., van den & Nicolaides K. H. (1990) Platelet count in normal, small, and anemic fetuses. *Am J Obstet Gynecol* **162,** 735–739.

Karas G. P., Rosse W. F. & Kurlander R. J. (1982) Characterization of the IgG-Fc receptor on human platelets. *Blood* **60,** 1277–1282.

Kiefel V., Santoso S., Weisheit M. & Mueller-Eckhardt C. (1987) Monoclonal antibody-specific immobilization of platelet antigens (MAIPA): a new tool for the identification of platelet-reactive antibodies. *Blood* **70,** 1722–1726.

Mir N., Samson D., House M. J. & Kovar I. Z. (1988) Failure of antenatal high-dose immunoglobulin to improve fetal platelet count in neonatal alloimmune thrombocytopenia. *Vox Sang* **55,** 188–189.

Mueller-Eckhardt C., Kiefel V., Grubert A., Kroll H., Weisheit M., Schmidt S., Mueller-Eckhardt G. & Santoso S. (1989) 384 cases of suspected neonatal alloimmune thrombocytopenia. *Lancet* **i,** 363–366.

Mueller-Eckhardt C., Mueller-Eckhardt G. & Willen-Ohff H. (1985) Immunogenicity of and immune response to the human platelet antigen Zw (a) is strongly associated with HLA-B8 and DR3. *Tissue Antigens* **26,** 71–76.

Muller J. Y. (1987) Neonatal alloimmune thrombocytopenia: clinical immunology and allergy. In *Alloimmune and Autoimmune Cytopenias* (Engelfried C. P. & Borne A. E. G. K. von dem., eds) Ballière Tindal, Philadelphia, pp. 427–442.

Murphy M. F., Pullon H. W. H., Metcalfe P. *et al.* (1990) Management of fetal alloimmune thrombocytopenia by weekly in utero platelet transfusions. *Vox Sang* **58,** 45–49.

Nicolini U., Tannirandorn Y., Gonzalez P., Fisk N. M., Beacham J., Letsky E. A. & Rodeck C. H. (1990) Continuing controversy in alloimmune thrombocytopenia: Fetal hyperimmunoglobulinemia fails to prevent thrombocytopenia. *Am J Obstet Gynecol* **163,** 1144–1146.

Reznikoff-Etievant M. F. (1988) Management of alloimmune neonatal and antenatal thrombocytopenia. *Vox Sang* **55,** 192–201.

Schneider W. & Schnaidt M. (1981) The platelet adhesion immunofluorescence test. A modification of the platelet suspension immunofluorescence test. *Blut* **43,** 389–392.

Shulman N. R. & Jordan J. V. Jr (1982) Platelet immunology. In *Hemostasis and Thrombosis: Basic Principles and Clinical Practice* (Colman R. W., Hirsh J., Marder V. J. & Salzman E. W., eds) J. B. Lippincott, Philadelphia, pp. 274–342.

Taaning E. & Skibsted L. (1990) The frequency of platelet alloantibodies in pregnant women and the occurrence and management of neonatal alloimmune thrombocytopenic purpura. *Obstet Gynecol Survey* **45,** 521–525.

Terasaki P. I. & McClelland J. D. (1964) Microdroplet assay of human serum cytotoxins. *Nature* **204,** 998–1000.

Weerdt C. M. van der, Veenhoven R. L. A. von, Nijenhuis J. E. & Loghem J. J. (1963) The Zw blood group system in platelets. *Vox Sang* **8,** 513–530.

Received 8 July 1991
Accepted 24 September 1991

British Journal of Obstretrics and Gynaecology
March 1992, Vol. 99, pp. 263–264

Successful twin pregnancy despite proven intraperitoneal chlamydial infection at implantation

P CURTIS
Infertility Clinical Research Fellow
N. AMSO
Infertility Clinical Research Fellow
Royal Free Hospital, London UK
R. M. PARNABY
Senior Registrar in Medical Microbiology
Central Middlesex Hospital, London, UK
C. C. KIBBLER
Consultant in Medical Microbiology
R. W. SHAW
Professor of Obstetrics and Gynaecology
Royal Free Hospital, London, UK

Case report

A 31-year-old woman presented with 7 years of secondary infertility. She had previously conceived an unplanned pregnancy with the same partner at the age of 16, but had had a miscarriage. She had never had any abdominal surgery, or pelvic infection, and laparoscopy and dye insufflation were normal.

She was treated with zygote intra-fallopian transfer (ZIFT) for unexplained infertility. After pituitary down-regulation and ovarian superovulation, oocyte collection was performed using vaginal ultrasound guided aspiration technique.

Three pronucleate embryos were replaced by ZIFT into the left fallopian tube, 24 h after egg collection. At the time of laparoscopy, the pelvis was noted to be normal. As part of a trial to assess the prevalence of infection following transvaginal oocyte collection, blood stained fluid was aspirated from the pouch of Douglas and samples were cultured for growth of bacteria and *Chlamydia*.

Immediate post-operative recovery was uneventful with no pyrexia or abdomino-pelvic pain. She returned home the following day and subsequently remained well, with no signs of infection.

The bacteriological culture grew no organisms but culture for *Chlamydia trachomatis* was positive.

The patient was asked to attend for examination and treatment. However, as she remained free of symptoms, an endocervical swab for *Chlamydia* culture and a serum sample for chlamydial antibodies were taken and treatment was deferred until the results were available.

The endocervical swab for *C. trachomatis* was negative and, while she was waiting for the results of serology, a pregnancy test was positive.

Twin intrauterine gestation sacs were detected by transvaginal sonography, 4 weeks after embryo replacement and subsequent scans confirmed a twin pregnancy.

Serum taken before and shortly after oocyte collection was negative for chlamydial antibodies by both immunofluorescence and group complement fixation test methods However, subsequent specimens showed equivocally raised levels of both IgG and IgM.

Both partners were treated with erythromycin 500 mg twice daily for 2 weeks. The pregnancy continued normally and spontaneous vaginal delivery of twin girls weighing 2585 g and 2670 g occurred at 37 weeks gestation. No sequelae of infection occurred in either the infants or their mother.

Discussion

C. trachomatis infection is frequently asymptomatic. It has been implicated as an important factor in cervicitis, endometritis, peritonitis, the Curtis-Fitz-Hugh syndrome, pelvic inflammatory disease and tubal causes of infertility (Sellors *et al.* 1988).

The method of diagnosis is important in determining the significance of detecting *C trachomatis*. The most sensitive and specific method is cell culture and this has been considered the standard method of confirming infection. However, it is expensive, time-consuming and technically difficult, and is often limited to larger laboratories.

Antigen detection is much simpler but suffers from a high rate of false positive results due to cross reaction with other micro-organisms. Similarly, direct cytological staining is of limited use because of false positive and false negative results (Sweet *et al.* 1983).

Serology lacks sensitivity and does not always correlate closely with clinical signs of infection (Schachter 1979). Raised antibody titres may indicate past infection, chronic low grade infection or even persistence of chlamydial antigens or of the organism in a non-infectious form (Lunenfield *et al* 1988). Comparison of group-specific complement fixing antibodies with immunofluorescence may be more sensitive in diagnosing active infection (Conway *et al.* 1984), but the place of serology as a method of diagnosis remains controversial (Smith *et al.* 1991).

More recently, DNA hybridization has been shown to be a sensitive and specific method which may be easier to perform and, ultimately, may become more widely available (Pao *et al.* 1987).

The site of infection is important in determining significance. Asymptomatic infection of the lower genital tract does not always cause ascending infection and damage. Evidence of prior infection can be demonstrated serologically in pregnant women and in infertile women with no tubal damage (Conway *et al.* 1984). Furthermore, endometritis occurs in only about a half of the patients with chlamydial cervicitis (Sellors *et al.*

Correspondence: P Curtis, Clinical Research Fellow, Academic Department of Obstetrics and Gynaecology, Royal Free Hospital, Pond Street, London NW3 2QG.

1988), and not all of these develop salpingitis (Cleary & Jones 1985). Endometritis can also occur in the absence of cervical infection (Cleary & Jones 1985). Nevertheless, prior chlamydial infection is associated with increased tubal damage and a subsequent need for IVF. It may also be associated with reduced success during IVF (Rowland *et al.* 1985), though this has not been supported by another study (Torode *et al.* 1987). Neither study showed a reduction in oocyte fertilization rates, so any adverse effects may be due to low grade endometritis or infection of the embryo preventing implantation (Rowland *et al.* 1985).

The effect of acute chlamydial infection has been questioned (Torode *et al.* 1987). While active infection may be present in pregnant women (Orsos *et al.* 1988) the infection may be limited to the cervix or acquired after the establishment of pregnancy. In-vitro fertilization and subsequent pregnancy can occur despite *C. trachomatis* contamination of the culture media (Kletter *et al.* 1988), but active maternal infection may disturb maturation of the embryo (Osser *et al.* 1990) and prevent endometrial implantation or cause ectopic pregnancy (Diquelou *et al.* 1988).

Though animal models have shown that normal pregnancy can occur during acute chlamydial infection (Svenson *et al.* 1986), we are unaware of any previous report of a successful human embryo implantation and pregnancy in the presence of culture-proven intraperitoneal chlamydial infection.

References

Cleary R. E. & Jones R. B. (1985) Recovery of chlamydia trachomatis from the endometrium in infertile women with serum antichlamydial antibodies. *Fertil Steril* **44,** 233-255.

Conway D., Glazener C., Caul E. O., Hodgson J., Hull M. G. R., Clarke S. & Stirrat G. M. (1984) Chlamydial serology in fertile and infertile women. *Lancet* **i,** 191-193.

Diquelou J. Y., Tesquier L., Henry-Suchet J., Pastorini E., Pia P. & Gicquel J. M. (1988) Positive cultures for chlamydia trachomatis in patients with ectopic pregnancy. (Abstr.) *Proceedings of the European Society for Chlamydia Research* (1988), Almqvist & Wiksell International, Stockholm, p. 190.

Kletter Y., Amster R., Lessing J. B. *et al.* (1988) Does active chlamydia trachomatis infection affect the success of IVF/ET treatment? (Abstr.) *Proceedings of the European Society for Chlamydia Research*, Almqvist & Wiksell International, Stockholm, p. 189.

Lunenfield E., Shapiro B. S., Sarov B., Sarov I., Inslr V. & Decherney A. H. (1988) The effect of chlamydia on pregnancy outcome in an in vitro fertilisation program. (Abstr.) *Proceedings of the European Society for Chlamydia Research* (1988), Almqvist & Wiksell International, Stockholm, p. 188.

Orsos M., Sziller I., Pulay T., Nasz S. & Csomor S. (1988) Cervical *Chlamydia trachomatis* infection and the chances of pregnancy. (Abstr.) *Proceedings of the European Society for Chlamydia Research* (1988), Almqvist & Wiksell International, Stockholm, p. 196.

Osser S., Persson K., Wrambsby H. & Liedholm P. (1990) Does previous *Chlamydia trachomatis* infection influence the pregnancy rate of in vitro fertilization and embryo replacement? *Am J Obstet Gynecol* **162**, 40-44.

Pao C. C., Lin S. S., Yang T. E., Soong Y. K., Lee P. S. & Lin J. Y. (1987) Deoxyribonucleic acid hybridisation analysis for the detection of urogenital *Chlamydia trachomatis* infections in women. *Am J Obstet Gynecol* **156,** 195-199.

Rowland G. F., Forsey T., Moss T. R., Steptoe P. C., Hewitt J. & Darougar S. (1985) Failure of in vitro fertilisation and embryo replacement following infection with *Chlamydia trachomatis. J In Vitro Fert Embryo Transfer* **2,** 151-155.

Schachter J., Cles L., Ray R. & Hines P. A. (1979) Failure of serology in diagnosing chlamydial infection of the female genital tract. *J Clin Microbiol* **10,** 647-649.

Sellors J. W., Mahony J. B., Chernesky M. A. & Rath D. J. (1988) Tubal factor infertility: an association with prior chlamydial infection and asymptomatic salpingitis. *Fertil Steril* **49,** 451-457.

Smith J. R., Murdoch J., Carrington D. *et al.* (1991) Prevalence of *Chlamydia trachomatis* infection in women having cervical smear tests. *Br Med J* **302,** 82-84.

Sweet R. L., Schachter J. & Landers D. V. (1983) Chlamydial infections in obstetrics and gynecology. *Clin Obstet Gynecol* **26,** 143-164.

Swenson C. E., Sung M. L., Schachter J. (1986) The effect of tetracycline treatment on chlamydial salpingitis and subsequent fertility in the mouse. *Sex Transm Dis* **13,** 40-44.

Torode H. W., Wheeler P. A., Saunders D. M., McPetrie R. A., Medcalf S. C. & Ackerman V. P. (1987) The role of chlamydial antibodies in an in vitro fertilization program. *Fertil Steril* **48,** 987-990.

Received 23 August 1991
Accepted 14 October 1991

British Journal of Obstetrics and Gynaecology
March 1992, Vol. 99, pp. 265–267

SHORT COMMUNICATIONS

Immunohistochemistry in pelvic nodes of patients with cervical cancer

GERALD GITSCH
ALEXANDER REINTHALLER
PETRA KOHLBERGER
GERHART TATRA
GERHARD BREITENECKER

2nd Department of Obstetrics and Gynaecology
University of Vienna Medical School, Spitalgasse 23,
A/1090 Vienna, Austria

During the years 1980-1986 a total of 158 women with cervical carcinoma stage Ia to IIB underwent Wertheim-Meigs operation at the 2nd Department of Obstetrics and Gynaecology, University of Vienna Medical School. Obturator and iliac lymph nodes were resected in all patients. In 111 the lymph nodes were histologically free of tumour. Ten of the 111 women developed tumour recurrence during a follow-up period of at least 5 years; three of them had histological stage IB and seven had stage IIB carcinoma at primary surgery. All of the stage IIB patients had irradiation therapy after surgery. Histology revealed eight squamous cell carcinomas, one adenocarcinoma and one muco-epidermoid carcinoma. In nine tumours vascular involvement was detected (we did not distinguish between veins and lymphatics, because the differentiation between these small vascular channels is often uncertain). Inflammatory stromal reaction at the tumour invasion front was pronounced in two of the carcinomas, moderate in three and weak in five. Routine histological and immunohistochemical procedures included the examination of all dissected lymph nodes at two or three levels.

The aim of our study was to assess the usefulness of immunohistochemistry for the detection of micrometastases in pelvic lymph nodes which had been judged negative by the pathologist.

Material and methods

Three monoclonal antibodies were tested in the primary tumours of the ten patients who developed tumour recurrence. In all ten the most reliable marker, with strong staining reactions was cytokeratin HMW (Enzo, NY, USA) specific for cytokeratins 1, 5, 10 and 11. This monoclonal antibody was then used for immunohistochemical staining in all of the dissected lymph nodes.

Paraffin sections were soaked in xylene to remove paraffin and rehydrated in graded alcohol series (100% to 70%). For enzyme predigestion of formalin-fixed tissue, the sections were incubated for 10 min at 37°C in 0·1 g Pronase type 14/100 ml phosphate-buffered saline (PBS) and then washed in 10 mM PBS (pH 7·6) and 0·1% TritonX100. The primary antibody was diluted in serum/PBS and the sections were incubated for 60 min and then incubated for a further 30 min with diluted biotinylated anti-mouse immunoglobulin (BioGenex, CA, USA). After rinsing in PBS, the sections were coated with diluted alkaline phosphatase-conjugated streptavidin (BioGenex). The sections were rinsed in PBS, incubated in alkaline phosphatase substrate solution (substrate: naphthol AS-MXphosphate in Tris/HCl-buffer, chromogen: tablets of Fast Red TR salt, BioGenex) and then washed with distilled water. The sections were finally counterstained with haematoxylin and mounted.

Results

Neither metastases nor micrometastases were found in any of the investigated lymph nodes. In one case we detected a tumour cell embolus in a venule beneath an external iliac lymph node (Fig. 1). This patient had a histological stage IB tumour which showed vascular involvement and moderate inflammatory stromal reaction.

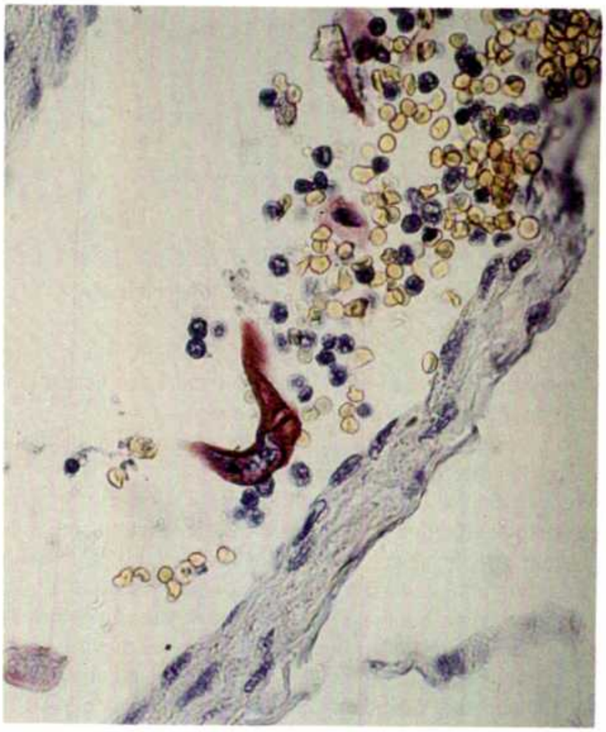


Fig. 1. Tumour cell embolus in a venule beneath an external iliac lymph node.

Correspondence: Dr Gerald Gitsch.

Discussion

Lymph node metastases are known to be one of the most reliable prognostic factors in cervical cancer, especially in stage IIB (Monaghan *et al.* 1990; Alvarez *et al.* 1989). As only 10% of our patients, who underwent Wertheim-Meigs operation and had negative lymph nodes, developed tumour recurrence, the presence of possible micrometastases was investigated. Since micrometastases and tumour cell emboli are difficult to detect and can easily be missed by routine histology, we used immunohistochemical methods to identify single tumour cells.

In none of the investigated lymph nodes could micrometastases be detected by immunohistochemical staining. In one case a tumour cell embolus of three tumour cells was detected in a small vein (Fig. 1). The tumour recurrence seemed, therefore, to be due to the relatively advanced stage of disease in most of the patients, and the presence of vascular involvement and weak or moderate inflammatory stromal reaction which are important prognostic factors (Baltzer *et al.* 1982; Reinthaller *et al.* 1991).

We conclude that immunohistochemistry can be a helpful tool to search for single tumour cells, if an adequate marker is used. As the prognostic value of tumour cell emboli is low, immunohistochemical methods do not appear to be an improvement on routine diagnostic procedures for the detection of nodal metastases in patients with cervical cancer.

References

Alvarez R. D., Soong S. J., Kinney W. K. *et al.* (1989) Identification of prognostic factors and risk groups in patients found to have nodal metastases at the time of radical hysterectomy for early stage squamous carcinoma of the cervix. *Gynecol Oncol* **35**, 130-135.

Baltzer J., Lohe K. J., Köpke W. & Zander J. (1982) Histological criteria for the prognosis in patients with operated squamous cell carcinoma of the cervix. *Gynecol Oncol* **13**, 184-187.

Monaghan J. M., Ireland D., Mor-Yosef S., Pearson, Lopes A. & Sinha D. P. (1990) Role of centralization of surgery in Stage IB carcinoma of the cervix: a review of 498 cases. *Gynecol Oncol* **37**, 206-209.

Reinthaller A., Tatra G., Breitenecker G. & Janisch H. (1991) Inflammatory stromal reaction and other prognostic determinant after radical hysterectomy in invasive cervical cancer stages IA to IIB. *Geburtshilfe Frauenheilk* **51**, 809-813.

Received 28 May 1991
Accepted 14 November 1991

British Journal of Obstretrics and Gynaecology
March 1992, Vol. 99, pp. 266–267

A comparison of two endometrial samplers

A. L. SHEEHAN
Senior Registrar in Histopathology
M. D. READ
Consultant in Obstetrics and Gynaecology
B. W. CODLING
Consultant Histopathologist
Gloucestershire Royal Hospital, Gloucester GL1 3NN

A leader in the *Lancet* (1979) concluded that endometrial sampling should be much more widespread.

A number of plastic disposable endometrial sampling devices have been introduced in the past five years. They are of two designs: the first is a flexible plastic sleeve in a piston which allows suction to be applied to draw a sample of endometrium into the sheath (Z-sampler and pipelle). The second cuts a sample of endometrium off with the rotation of a blade which is then withdrawn into a flexible sheath (Gynocheck).

This study was undertaken to compare these two types of devices to determine if one was significantly and consistently better than the other at obtaining samples suitable for diagnosis.

Correspondence: A. L. Sheehan.

Subjects and methods

The study included 100 premenopausal women over the age of 35 years (mean age 43 years; range 36–55 years) who attended the outpatient gynaecology clinic of one consultant and who were considered to require an endometrial biopsy. Premenopausal women were chosen to maximize the amount of endometrium available for biopsy, as postmenopausal atrophic endometrium often yields scanty material.

Two biopsies were taken from each woman, one using the Gynocheck (G) (Roussel), the other using the Z-sampler (Z) (Cory Bros). To eliminate bias, the order in which the biopsies were taken was randomized, so that 50 women were sampled first with the Gynocheck and 50 first with the Z-sampler. The allocation was in sealed opaque envelopes that were opened immediately before sampling. The paired biopsies were labelled 1 and 2 by the gynaecologist with no reference to the sampler used.

The biopsies were fixed in 10% buffered formalin for 24 h; all the material obtained was processed. Paraffin sections 4 μm thick were cut and stained with haematoxylin and eosin. Three sections were cut at intervals through the paraffin block and the section displaying the maximum amount of material was used for the study. The quantity of curettings obtained was assessed by the area on a microscope slide. If a biopsy covered less than one-quarter of the surface area of a 2·2 cm × 2·6 cm coverslip,

Table 1. McNemar's test for comparison of paired endometrial samples recorded by two histopathologists, A and (B)

	Gynocheck		
	Inadequate and small	Medium and generous	Total
Z-sampler	A (B)	A (B)	A (B)
Inadequate and small	23 (32)	9 (7)	32 (39)
Medium and generous	52 (53)	15 (7)	67 (60)
Total	75 (85)	24 (14)	99 (99)

Total of 99 women. Each woman counts as one unit in the table. For each pathologist, A & (B), McNemar's test was highly significant ($P<0{\cdot}001$).

it was termed small; a quarter to three-quarters was termed medium and greater than three-quarters was regarded as generous. Tiny fragments of endometrium too small for adequate histological assessment were called inadequate.

Each biopsy was examined by two histopathologists (A and B) both of whom recorded the quantity and diagnosis independently. A comparison of quantities recorded by the two histopathologists was made using the Kappa statistics (Cohen 1960). McNemar's test for matched or paired samples was used to compare the Z and G samples from each woman (Bland 1987). As medium and generous biopsies were adequate for diagnosis, these numbers were combined; similarly small and inadequate numbers were combined.

Results

Paired samples were obtained from 99 of the 100 women. It was not possible to obtain samples from one woman because of cervical stenosis following an earlier cone biopsy. She was therefore excluded from the analyses.

Kappa statistics showed excellent agreement for quantitation between the two pathologists results. Direct correlation for the first biopsy was 80 out of 99; K = 0·71 and for the second biopsy 84 out of 99; K = 0·78 (0·75 indicates excellent agreement, 0·4 indicates poor agreement). This ruled out the possibility that one pathologist was consistently over or under quantifying. It also proved that the method for quantitation was reproducible.

Table 1 shows the paired results for each woman by both pathologists in the size categories 'inadequate' and 'small' *vs* 'medium' and 'large' for each sampler. McNemar's test for these paired samples was highly significant ($P<0{\cdot}001$) indicating that there was a difference in the quantity of material obtained. Whether the Z-sampler was used first, or second after the Gynocheck was immaterial as medium and generous biopsies were obtained in 65% and 63% of cases by the Z-sampler. However, medium and generous biopsies were only obtained in 29% of the first Gynocheck biopsies and in 10% of the second Gynocheck biopsies. Therefore the Z-sampler produced significantly better samples than the Gynocheck sampler.

Discussion

Outpatient endometrial samplers are acceptable to patients (Eddowes *et al.*, 1990) and do not require a general anaesthetic.

The use of a sampler that is less likely to yield an inadequate biopsy reduces the necessity for a second biopsy, which not only lowers costs but also saves the patient the added worry of a repeat biopsy.

Our results show that the Z-sampler obtained significantly larger amounts of endometrium for diagnosis than the Gynocheck sampler. Larger biopsies facilitate diagnosis and ensure that the biopsy is more likely to be representative of the endometrium as a whole.

References

Bland M. (1987) In *An Introduction to Medical Statistics*. Oxford Medical Publications, Oxford, pp. 255–258.

Cohen J. A. (1960) A coefficient of agreement for nominal scales. *Educational and Psychological Measurement* **20**, 37–46.

Eddowes H. A., Read M. D. & Codling B. W. (1990) Pipelle: a more acceptable technique for outpatient endometrial biopsy. *Br J Obstet Gynecol* **97**, 961–962.

Lancet leader (1979) Outpatient uterine curettage. *Lancet* **i**, 1174.

Received 20 May 1991
Accepted 2 December 1991

British Journal of Obstetrics and Gynaecology
March 1992, Vol. 99, pp. 268–270

BLAIR BELL RESEARCH SOCIETY

Papers presented at the meeting on 29 April 1991 at the Royal College of Obstetricians and Gynaecologists

Colposcopically directed punch biopsy: a misleading investigation? by E. J. Buxton, D. M. Luesley, T. P. Rollason, M. I. Shafi and C. W. E. Redman. University of Birmingham, Department of Obstetrics & Gynaecology, Dudley Road Hospital, Birmingham, West Midlands.

Selecting women with cervical intraepithelial neoplasia (CIN) for local destructive treatment relies on colposcopic assessment of the cervical transformation zone and histological appraisal of a directed biopsy from the area of most severe epithelial abnormality. The ability of the colposcopist to determine accurately the severity of CIN and even diagnose early invasion has been questioned. We analysed data from 243 patients managed by colposcopy and directed punch biopsy, followed by outpatient loop diathermy excision of the cervical transformation zone. We determined the correlation between the initial directed biopsy and the histology in the excised transformation zone to investigate the effect of a subjective assessment of the lesion size. Patients with cytological or colposcopic evidence of invasion were excluded from this analysis. In 132 of 243 women (54%) the results of the punch biopsy did not agree with those of the subsequent loop excision specimen. In 70 of 132 women (53%) the severity of the lesion found in the punch biopsy was greater than that in the loop excision specimen and in 62 (47%) a more severe lesion was found in the excised transformation zone, including three with previously unsuspected adenocarcinoma *in situ* (AIS), and one with Ia(i) invasive cancer. In 39 of 96 women (41%) in whom a high grade lesion (CIN 3, AIS, or stage Ia(i)) or greater severity was found in the loop excision specimen, the paired punch biopsy specimen suggested the lesion to be of lesser severity. In 25 of these 39 women (24 CIN 3, and 1 AIS) the total lesion occupied no more than four sectors. In the remaining 14 (11 CIN 3, 1 stage Ia(i) and 2 AIS) the total lesion occupied five or more sectors. The likelihood of discrepancy between the punch biopsy and loop excision specimen was significantly associated with overall lesion size. The punch biopsy was more likely to overcall severity in small area lesion ($P = 0{\cdot}0005$). The likelihood of the punch biopsy undercalling the severity of the lesion was not significantly associated with lesion size. These results suggest that directed punch biopsy is an inadequate endpoint by which to judge the severity of an epithelial lesion before local destructive treatment of the cervical transformation zone. These findings have important implications both for patient management and for trial design and must cast doubt on the results of studies in preinvasive disease using directed punch biopsy as an endpoint.

Effects of plasma oestradiol levels on increases on vertebral and femoral bone density following therapy with oestradiol and oestradiol with testosterone implants by T. J. Garnett, J. W. W. Studd, N. R. Watson, M. Savvas, A. Leather and A. Henderson. Dulwich Hospital, East Dulwich Grove, London SE22 8PT

Oestradiol implants preserve the bone density of post-menopausal women. However, they are often given with testosterone which may itself have an anabolic effect on bone. Fifty post-menopausal women were randomly allocated to receive implants of either oestradiol (75 mg) or oestradiol with testosterone (100 mg) every 6 months for 1 year. They were matched with a group of 25 untreated women to act as a reference group. Bone density was measured at the lumbar spine and proximal femur by dual X-ray densitometry (Hologic). At 1 year bone density decreased at the lumbar spine by 1·8% in the reference group but increased by 7·8% in those treated with oestradiol and by 6·3% in the patients receiving oestradiol with testosterone (both $P<0{\cdot}001$). The increase in bone density was significantly correlated with the serum oestradiol levels achieved at 1 year of therapy ($r = 0{\cdot}4$, $P<0{\cdot}01$). Testosterone confers no additional bone sparing effect in post-menopausal women and the increase in bone density after 1 year was correlated with serum oestradiol levels.

Multicentre assisted delivery trial by R. B. Johanson, C. Rice, M. Doyle, J. Arthur, L. Anwanyu, J. Ibrahim, A. Warwick and P. M. S. O'Brien. Department of Obstetrics & Gynaecology, Keele University, Staffs.

Vacca & Keirse (1989) In *Effective Care in Pregnancy and Childbirth* (Chalmers I., Enkin M. & Keirse M. J. N. C., eds) Oxford University Press, p. 1216), in their review of the randomized controlled trials between forceps and the ventouse found that in all studies forceps were significantly more likely to injure the mother. A policy has been devised to optimize the ventouse success rate and minimize morbidity, by the appropriate usage of the Silc-cup and Bird anterior and posterior cups. A four centre randomized comparison between forceps and this new 'vacuum extractor policy' was undertaken. A sample size of 650 deliveries was required, 296 women were allocated to be delivered by ventouse and 311 by forceps. The preliminary results of ventouse ($n = 296$) *vs* forceps ($n = 311$) deliveries showed a successful delivery in 251 (85%) *vs* 279 (90%), odds ratio 0·6 (95% CI 0·4–1); a three or four degree tear in 32 (11%) *vs* 52 (17%) odds ratio 0·6 (95% CI 0·4–1); general or regional anaesthesia in 135 (46%) *vs* 232 (75%), odds ratio 0·3 (95% CI 0·2–0·5) ($P<0{\cdot}05$); cephalhaematoma in 27 (9%) *vs* 8 (3%), odds ratio 3·8 (95% CI 1·7–8) ($P<0{\cdot}05$) and phototherapy in 3 (1%) *vs* 7 (2%) (non significant). In addition there were 32 babies born by forceps with facial bruises, three with facial cuts and three with unexplained neonatal convulsions. The new 'vacuum extractor policy' resulted in a satisfactory success rate and the occurrence of maternal injury and cephalhaematoma were similar to those at previous studies. Further studies will be required to assess the relative effects of the two instruments in terms of major neonatal morbidity.

Umbilical vein blood pressure and cardiac size in non-immune hydrops by P. Johnson, G. Sharland, L. Allan, M. Tynan and D. Maxwell. Guy's Hospital, London SW1 9RT

Intrauterine cardiac failure is believed to be the commonest mechanism underlying non-immune hydrops fetalis. In adults cardiac failure is associated with relevation of central venous pressure and cardiac enlargement, and these changes are believed to occur in the fetus. Fetal cardiac size can be assessed by measuring the cardiothoracic ratio. Umbilical vein blood pressure, which reflects central venous blood pressure, can be measured at the time of fetal blood sampling. In a series of 17 fetuses with non-immune hydrops, cardiothoracic ratio and vascular pressure were recorded in 13 fetuses, from the umbilical vein in 10, from the umbilical artery in two and from the right atrium in one. In eight fetuses who had associated ascites, the umbilical vein blood pressure was elevated (10–16 mm Hg, normal range 1–6) and the cardiothoracic ratio was significantly raised ($P = 0{\cdot}02$). The other two fetuses with umbilical vein blood pressure measurement but no ascites, had umbilical vein blood pressures and cardiothoracic ratios within the normal range. The correlation of venous pressure with the cardiothoracic ratio validates the ratio as non-invasive assessment of the cardiac function.

Tuboscopic findings in normal women by S. D. Maguiness & O. Djahanbakch. Academic Unit of Obstetrics & Gynaecology, The London Hospital Medical College, Newham General Hospital, Glen Road, Plaistow, London E13 8RU

To establish normal variation in the appearance of the fallopian tube lumen 36 consecutive women undergoing sterilization, who had had normal fertility, gave consent for tuboscopy. At laparoscopy, 12 women had pelvic pathology, adhesion in 10 and endometriosis in two, and they were excluded from the study. Of the remaining 24 women 23 had bilateral tuboscopy and one a unilateral tuboscopy because of a distal tubal occlusion. The observations made included intratubal adhesions in one tube ($n = 2$), fronds attached to the edge of the folds bilaterally ($n = 3$), flattening of the mucosal folds ($n = 1$), vessels with an irregular lumen ($n = 2$) and black spots ($n = 2$). The mucosal fold edges appeared rounded and the blood vessel walls brightly reflective in three women who were within 4 days of ovulation. There did not appear to be any correlation between the appearance of the fallopian tube lumen and the use of any form of contraception or the previous reproductive history. These observations in women who had experienced normal fertility must be considered when tuboscopy is used to investigate a fertility problem.

Allo-MHC specific anti-parental cytotoxic T cell immunity in women with recurrent miscarriage by I. Manyonda, S. Pereira, J. M. Pearce, C. Sharrock. Department of Immunology and Gynaecology, St George's Hospital Medical School, London SW17

Anti-paternal cytotoxix T lymphocyte frequencies were determined by limiting dilution analysis in the peripheral blood of 10 women with recurrent miscarriage is (defined as three consecutive miscarriages with the same partner, no more than one living child) before and after immunization with paternal lymphocytes (the latter were administered as therapy for the repeated miscarriages). The women and their partners were all HLA tissue-types and none of the women had anti-paternal cytotoxic antibodies before immunization. All other known causes of recurrent miscarriage were excluded. All the women were found to have high frequencies of specific anti-paternal cytotoxic T cells before immunization and in all of them the frequencies rose after immunization. There was no correlation between the formation of anti-paternal cytotoxic antibodies and the frequency of cytotoxic T cells. The cytotoxic T lymphocyte frequencies against a constant third party were variable from woman to woman, but they were not significantly affected by the immunization. The limiting dilution data conformed to single-hit kinetics, indicating that only cytotoxic T cells were limiting in the assay. Specificity was determined using split-well analysis. These findings indicate maternal T-cell activation following immunization.

Association between fetal distress and myocardial conduction defect during human labour by M. P. Mohajer, D. Sahota and E. M. Symonds. Queen's Medical Centre, Nottingham

Since the initial description over 80 years ago, the fetal electrocardiogram (FECG) has been investigated for its potential to reflect myocardial changes related to perinatal asphyxia. With the advent of new computer techniques allowing for improved isolation and analysis, the FECG has been reassessed as a means of fetal surveillance during parturition. In this study, a minicomputer developed by the electronic engineering department at Nottingham University has been used for on-line analysis of the FECG waveform. The ECG signal is obtained from the fetus via a conventional fetal scalp electrode. This is fed into a Sonicaid FM3R monitor, which provides electrical isolation for the fetus and a CTG record for the labour ward staff. The signal is then processed by a computer system to restore the low frequency components of the FECG, and enhanced by a software-based time-coherent averaging routine. Overall, 120 fetuses were monitored during labour, 14 developed 'fetal distress' as shown on the CTG by severe decelerations or bradycardia of <60 beats/min. Analysis of the ECG in these fetuses showed disappearance of P waves indicating sinus arrest and the establishment of nodal rhythm. Of the 14 fetuses 10 had biochemical evidence of anaerobic metabolism at birth. These findings suggest that conduction defects may indicate fetal compromise.

Vaginal temperature for measurement of circulatory changes in pelvic conditions by R. W. Stones, D. C. Thomas & R. W. Beard. Department of Obstetrics & Gynaecology, St Mary's Hospital Medical School, London W2 1PG

Vaginal temperature has been used to study variations in perfusion in the reproductive organs. Women with pelvic pain frequently have evidence of pelvic venous congestion which may involve a disturbance of neurovascular control mechanisms. Vaginal temperature (Tvag) was measured using a self-inserted thermistor probe with a resolution of 0·002°C in eight volunteer subjects and 12 women, with pelvic pain due to congestion. Core temperature was measured using a similar probe positioned in the axilla (Tax) and results expressed as the difference Tvag-Tax. Symptoms of pelvic discomfort or pain were recorded using 10 cm visual analogue scales and the scores were analysed using confidence intervals for the difference in median scores. Subjects lay supine during a 2-h observation period. After a 40 min control period with an inert infusion vasoactive intestinal polypeptide (VIP), 50 ng/kg/min, or calcitonin gene-related peptide (CGRP), 16 ng/kg/min, were infused over 15 min. All subjects experienced facial flushing. A consistent fall in Tvag-Tax was observed following infusion of VIP or CGRP. Visual analogue pain scores in women with pelvic congestion increased by 2 cm (96% CI 0·25–4·8) after VIP infusion but returned to baseline at 2 h.

Insulin resistance in polycystic ovarian syndrome by J. S. Samra, M. S. Obhrai, C. Lynch and J. Tighe. Birmingham Maternity Hospital, Edgbaston, Birmingham B15 2TG

Polycystic ovarian syndrome (PCOS) is characterized by a state of hyperandrogenism, excess serum levels of testosterone (T), androstenedone (A), 17 hydroxyprogesterone (17-OHP) and dehydroxyepiandosterone sulphate (DHEAS) and excess gonadotrophin secretion (increased LH, LH-FSH ratio). Recently a state of functional hyperinsulinaemia has been demonstrated in patients with PCOS. As yet it remains to be conclusively established whether (i) hyperandrogenism causes hyperinsulinaemia or (ii) hyperinsulinaemia causes hyperandrogenism in PCOS. In an attempt to clarify this point, we studied 15 women with PCOS and a control group of 15 women with normal ovulatory activity. The women had a 75 mg oral glucose tolerance test (OGTT) after a 12-h fasting state in the follicle phase of the cycle. Fasting blood samples were taken for determination of LH, FSH, E (oestrogen), A, 17-OHP, DHEAS, insulin and glucose. The women with PCOS were treated with intramuscular goserelin (Zoladex), a GnRH analogue, every 4 weeks for 20 weeks and then had a repeat oral glucose tolerance test. We found raised levels of T, A, 17-OHP, DHEAS, and LH in the women with PCOS and they also had hyperinsulinaemia. After treatment with goserelin there was a significant fall in the levels of T, A, and 17-OHP, but there was no change in the state of functional hyperinsulinaemia. There were significant correlations between hyperinsulinaemia and levels of T, 17-OHP, A, and DHEAS. Functional hyperinsulinaemia associated with PCOS persisted following a significant reduction in circulating androgens. Hyperinsulinaemia may be the most important factor in the pathogenesis of PCOS.

Development of customised charts for assessment of growth and birth centiles by J. Gardosi, A. Chang, B. Kalyan, P. Maynard & E. M. Symonds. Queen's Medical Centre, Nottingham

It is well-known that infant birthweights vary with maternal characteristics, but the growth curves and centile charts we use do not take account of this variation. We set out to design a combined birth centile/antenatal chart which can be easily customized for each individual pregnant women at booking. Computerized antenatal records of deliveries at the Queen's Medical Centre over the last 3 years were analysed for mean birthweights and correction factors. Apart from gestation and sex, the maternal height and booking weight, parity and ethnic group were identified as independent variables affecting birthweights in our population. A computer programme was written which used this information as a database, and calculated 'customized' 10th, 50th and 90th centile curves for the individual woman utilizing these six variables. The software can be adapted to include additional variables as well and for means and loading factors from different populations. It is designed to be used in the antenatal clinic after the routine scan has confirmed the dates; details of the current pregnancy, previous babies and maternal characteristics are entered, and the chart is then printed and added to the notes. The chart shows the clinician at a glance whether previous babies were appropriate weight-for-gestation. A second, non-linear scale of fetal abdominal circumference is printed on the birthweight axis; thus ultrasound measurements during the current pregnancy can be plotted as they are made to give the estimated fetal weight and the centile value, customized to that woman's characteristics. We have shown in a preliminary, retrospective study that abnormal growth patterns are inadequately diagnosed if maternal characteristics are not taken into consideration. For example intrauterine growth retardation may be over diagnosed by 28%, resulting in unnecessary investigations (serial scans, Doppler), admissions for increased monitoring and intervention (induction of labour, operative deliveries). We have started a clinical trial to investigate the effect that the introduction of such a customized chart has on antenatal care.

The new official journal of the Society for Minimally Invasive Therapy

Minimally Invasive Therapy

Editor: John Wickham

Assistant Editors: M J Coptcoat, A Adam, E vanSonnenberg, J M Fitzpatrick

Since the founding of the Society for Minimally Invasive Therapy in 1989, the subject has gained rapidly in prominence and importance. A large number of surgeons, radiologists and clinicians are now just beginning to appreciate the benefits both to patients and practitioners, of minimally invasive techniques. *Minimally Invasive Therapy* will include innovative research papers, expert review articles, topical leading articles, instrumental studies and correspondence. The Editors aim to establish *Minimally Invasive Therapy* as a prestigious base from which workers in any speciality may present their experience for the benefit of their colleagues and patients.

Minimally Invasive Therapy will be published bimonthly from November 1991. Subscription prices for Volume 1, 1991/2, are as follows: Individual £75.00 (Europe), £86.00 (Overseas), US$173.00 (USA & Canada); Institutional £112.00 (Europe), £129.00 (Overseas), US$258.00 (USA & Canada).

All members of the Society for Minimally Invasive Therapy will receive the journal as part of their annual dues. Further details regarding the Society can be obtained from: Miss Fay Harrison, Society for Minimally Invasive Therapy, 25 John Street, London WC1N 2BL, UK.

ORDER FORM

☐ Please enter my 1991/2 ☐ institutional ☐ individual subscription to *Minimally Invasive Therapy*

☐ Please send me a FREE sample copy of *Minimally Invasive Therapy*

☐ I enclose a cheque (*made payable to Blackwell Scientific Publications Ltd*) for the sum of £ .... US$ ....

☐ I wish to pay by credit card. Please debit my American Express / Diner's Card / Mastercard / Visa card number ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

expiry date .... with the sum of £ .... US$ ....

Signature .... Date ....

Name ....

Address ....

Street/PO Box ....

Town & County/State ....

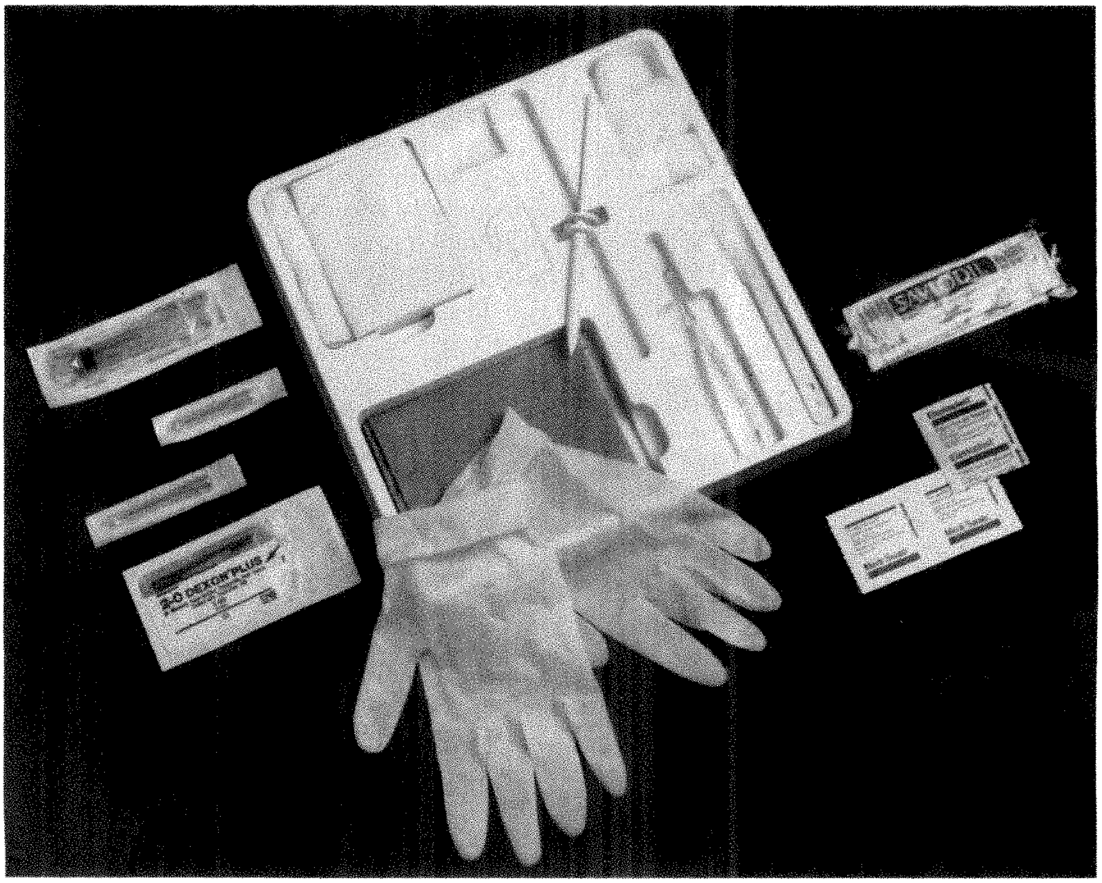
Country .... Post / Zipcode ....

BSP JOURNALS

Blackwell Scientific Publications
Osney Mead, Oxford OX2 0EL, UK

HORMONE REPLACEMENT THERAPY

A CONVENIENT STERILE DISPOSABLE TRAY WHICH
ENSURES A SIMPLE PROCEDURE REMAINS JUST THAT



IDEAL FOR USE IN HOSPITALS/CLINICS AND DOCTORS ROOMS

ORDER DETAILS:
HRT 851 HRT TRAY COMPLETE
HRT 853 HRT TRAY WITHOUT SUTURE MATERIAL

EURO SURGICAL LIMITED
The Common, Cranleigh,
Surrey GU6 8LU, U.K.
Telephone: 0483 267363.
Fax: 0483 267281.

Please send me more information on the HRT Tray.

Name ______________________
Title ______________________
Address ______________________
____
Telephone ______________________

British Journal of Obstetrics and Gynaecology
March 1992, Vol. 99, pp. 271–272

CORRESPONDENCE

Fetal blood sampling and pregnancy loss in relation to indication

Dear Sir,

The conclusion reached by Maxwell *et al.* (1991) that the risk of fetal blood sampling is increased in abnormal pregnancies is not valid. What they have described are four groups of complicated pregnancies that have different pregnancy losses. The primary reason is the underlying pathology and the authors acknowledge this. In the discussion they stress that it is uncertain as to how much of the increased loss in the complicated pregnancies is due to the procedure or to the natural history of the disease. Indeed, in the case of non-immune hydrops the intrauterine death rate described in the literature before the days of cordocentesis has been reported to be 51% (Gough *et al.* 1986), and this is not higher than described here (13/29 = 45%). In the authors' words, there was no control group in which no procedure was performed so a precise procedure-related risk cannot be established for any of the groups in the study.

D. Economides
Nuffield Department of Obstetrics and Gynaecology
John Radcliffe Hospital
Maternity Dept
Oxford OX3 9DU

References

Maxwell D. J., Johnson P., Hurley P., Neales K., Allan L. & Knott P. (1991) Fetal blood sampling and pregnancy loss in relation to indication. *Br J Obstet Gynaecol* **98**, 892–897.

Gough J. D., Keeling J. W., Castle B., Ilife P. J. (1986) The obstetric management of non-immunological hydrops. *Br J Obstet Gynaecol* **93**, 226–234.

Author's reply

Dear Sir,

We thank Mr Economides for his comments. We stated in our article that the principal aim of the analysis was to provide information that might be helpful in prospective counselling before fetal blood sampling is undertaken. The data show that pregnancy losses following fetal blood sampling are higher in abnormal pregnancies. Whatever the cause, we believe that this is important information to be taken into account when counselling patients before any intended procedure.

Darryl J. Maxwell
Director
Fetal Medicine Unit
Guy's Hospital
15th Floor Guy's Tower
London Bridge
SE1 9RT

Symptoms analysis for the diagnosis of genuine stress incontinence

Dear Sir,

In their recent article Versi *et al.* (1991) concluded that 'All women presenting with incontinence should undergo pre-operative urodynamic studies'. For a fit woman where surgery is a clear option this may be true. I would suggest that such a counsel of perfection is of little help where a professional judgement is required on the need, or otherwise, for a very distressing investigation in an unfit elderly lady.

In such a case, an answer to the title of the paper would have been more helpful, since Fig. 1 shows that, despite the central overlap, high or low scores can, as we all know, provide useful information. In their paper they say that Fig. 1 was based on a statistical technique which weighted 'the importance of any given symptom to obtain the greatest possible discrimination between patients with urethral sphincter incompetence and those without'. Could the authors therefore be prevailed upon to provide a list of these weightings?

Although this would not be relevant for most patients, it would increase the value of a careful history in the individual patient where urodynamic studies might cause unnecessary trauma for a patient whose weighted clinical analysis strongly indicated against the likelihood of useful surgery.

Rupert Fawdry
Honorary Senior Lecturer, University of London
Department of Obstetrics and Gynaecology
Milton Keynes General Hospital
Eaglestone
Milton Keynes MK5 6LD

References

Versi E., Cardozo L., Anand D. & Cooper D. (1991) Symptoms analysis for the diagnosis of genuine stress incontinence. *Br. J. Obstet Gynaecol* **98**, 815-819.

Author's reply

Dear Sir,

The data presented in our paper was collected from a urodynamic unit in a London teaching hospital. The prevalence of symptoms and urodynamic pathology in this population may not be the same as that for patients in other settings as was pointed out in our discussion. Therefore, application of our discriminant coefficients to other situations is, at present, premature. However, in the future, with corroboration of our results from other units, it may be possible to construct a universal model.

The main thrust of our paper was to examine the value of symptoms analysis for the diagnosis of genuine stress incontinence. Whereas the method presented is more accurate than any other clinical method published to date, the overall accuracy was not satisfactory, thus reinforcing the place of urodynamic studies.

Eboo Versi,
Senior Lecturer/Honorary Consultant
UMDS Department of Obstetrics and Gynaecology
St. Thomas's Hospital
Lambeth Palace Road
London SE1 7EH

The effect of maternal anaemia and iron deficiency on the ratio of fetal weight to placental weight

Dear Sir,

I read with interest the suggestion by Godfrey *et al.* (1991) that 47% of the pregnant population of Oxford are iron deficient. The Oxford region is one of the most affluent areas of the United Kingdom with one of the lowest perinatal mortality rates, and so the suggestion that such a high proportion of women still have an inadequate diet is disturbing. However, on further examination, their conclusion is questionable. It is based on the fact that women with haemoglobin levels below 11 g/dl and/or a fall in mean cell volume of >6 fl in pregnancy have an elevated ratio of placental weight to birthweight. Barker *et al.* (1990) have shown in a population of 449 men and women born in Preston during 1935–1943 and still living in Lancashire that having a large placenta is associated with an increased risk of systolic hypertension in later life. However, the risk of hypertension falls as birthweight increases. Thus, the highest risks of hypertension occur in small babies with large placentas. As placental weight and birthweight are highly correlated (Barker *et al.* 1990), anything which increases both will have an effect on blood pressure in later life which may be positive or negative, depending on the balance between the two effects. Godfrey *et al.* (1991) have confirmed the now well established fact that the lowest haemoglobin levels were associated with the highest birthweights, as well as the largest placentas. High haemoglobin levels are associated not only with lower birthweight, which is the major factor determining infant mortality (Leon 1991), but also with an increased risk of maternal complications such as hypertension (Murphy *et al.* 1986). A recent randomized controlled trial of iron supplementation in pregnancy (Hemminki & Rimpela 1991), the largest ever performed, suggested that the association between haemoglobin and packed cell volume and fetal growth was mediated through pregnancy induced plasma volume expansion (or lack of it) and that fetal growth was unrelated to iron metabolism. No advantages from routine supplementation of the diet with iron were demonstrated in their study.

Thus the risk to the larger baby of the mother with the lower haemoglobin level of having an even larger placenta, and thus possibly an increased risk of hypertension aged 60, may be balanced by a lower infant mortality. In addition, I note that Godfrey *et al.* (1991) show that the lower the maternal body mass index, the smaller the placental/birthweight ratio, and that the effect is similar in magnitude to that associated with haemoglobin variation. They do not, however, suggest that maternal underweight in pregnancy is advantageous.

The whole of life is a series of compromises, and it may be that factors advantageous to future reproductive potential (such as adaptations promoting survival during infancy) may have less welcome effects once the natural reproductive years are past. Thus one should exercise extreme caution before assuming that evolution has got it wrong, as interference may correct a small problem and produce a larger one.

Philip Steer
Professor
Department of Obstetrics & Gynaecology
Charing Cross & Westminster Medical School
West London Hospital
Hammersmith Road
London W6 7DQ

References

Barker D. J. P., Bull A. R., Osmond C. & Simmonds S. J. (1990) Fetal and placental size and risk of hypertension in adult life. *Br Med J* **301**, 259–262.

Hemminki E. & Rimpela U. (1991) Iron supplementation, maternal packed cell volume, and fetal growth. *Arch Dis Child* **66**, 422–425.

Godfrey K. M., Redman C. W. G., Barker D. J. P. & Osmond C. (1991) The effect of maternal anaemia and iron deficiency on the ratio of fetal weight to placental weight. *Br J Obstet Gynaecol* **98**, 886–891.

Leon D. A. (1991) Influence of birth weight on differences in infant mortality by social class and legitimacy. *Br Med J* **303**, 964–967.

Murphy J. F., O'Riordan J., Newcombe R. G., Coles E. C. & Pearson J. F. (1986) Relation of haemoglobin levels in first and second trimesters to outcome of pregnancy. *Lancet* **i**, 992–995.

Management of prolonged pregnancy—an analysis of women's attitudes before and after term

Dear Sir,

The recent paper by Roberts & Young (1991) on the management of prolonged pregnancy addressed an important issue in that we need to know the consumer's view. There are, however, a few methodological problems with their research.

The idea of conservative management was first mentioned to patients at 37 weeks gestation. By that time they would already have the expectation of being delivered by their expected date of delivery. If, however, they had been told, at their initial booking visit, that their pregnancy could continue for up to 44 weeks, perhaps they would have been more amenable to conservative management.

Following a change of policy, conflicting advice from other health workers, family and friends, about the dangers of prolonged pregnancy, would also bias the women's attitudes. The statement in the patient information sheet, indicating that there was no guarantee that pregnancies after 42 weeks did not carry a greater risk, will not have mitigated against this bias.

There appears to be a slight error in the calculations. The number of women who had, at 37 weeks, been in favour of conservative management, but had revised their preference by 41 weeks was 16 according to Table 2, but Table 4 states that this figure is actually 18.

Clearly a larger, more controlled, study is required to address this issue.

Marina Choudhury
Medical Student
Eboo Versi
Senior Lecturer/Honorary Consultant
UMDS Department of Obstetrics and Gynaecology
St Thomas's Hospital
Lambeth Palace Road
London SE1 7EH

British Journal of Obstetrics and Gynaecology
March 1992, Vol. 99, pp. 273–274

BOOK REVIEWS

Reproductive Endocrinology, Third edition edited by Samuel S. C. Yen & Robert B. Jaffe. W. B. Saunders Co., Philadelphia, 1991, 1016 pages, with figures and tables, £90.00

The third edition of this cornerstone of Reproductive Endocrinology by Yen & Jaffe sets out to 'reflect the striking advances in both the biological and clinical spheres' of the subject. The most significant advance has been in the basic understanding of cellular and nuclear mechanisms made possible by the powerful technology of molecular biology. The latter subject makes most clinicians despair of ever understanding these complex processes. This book contains new chapters and sections dedicated to the subject that are comprehensible and made easier by clear, well labelled diagrams with detailed legends. The section on steroid hormones and their receptors is particularly clear and will serve, for many readers, as the bedrock of knowledge they require to continue to increase their understanding of the reproductive process.

The expansion of the other chapters has, with few exceptions, resulted in a significant updating of current knowledge from the 1986 edition. The chapter on the endometrium with a review of current thinking on endometriosis is particularly comprehensive. Eli Adashi's review on the physiology of the ovarian life cycle with its additional sections on paracrine regulators of follicular development is enlightening. The advances in neuroendocrinology and in male reproductive endocrinology are also well represented. The inclusion of a section on surgical aspects of infertility is welcome as it begins to reflect the interest that both physicians and gynaecologists have in reproductive endocrinology. The section on ovulation induction and assisted conception is rather perfunctory which is disappointing as the endocrinology of early conception is advancing rapidly.

The impression gained from this book is that the expansion in the understanding of basic sciences is galloping while the clinical applications lag behind. This may reflect sensible caution on the part of clinicians but may also highlight the difficulty busy clinicians face in keeping pace with the changes. The rapidity of all these advances, particularly the scientific ones, is acknowledged in the preface yet the latest reference for any chapter is from 1988. The authors of the chapters are indeed at the 'cutting edge' of their subjects but the blade is considerably blunted by the long editorial and publishing process resulting in a three year delay. The third edition has certainly made substantial progress into the molecular age since 1986 but should be seen as a reference/teaching book for those interested in or new to the subject rather than representing the forefront of research. Nonetheless Reproductive Endocrinology rightfully remains the leader in its field both in terms of content and readability making it a must for all libraries and most reproductive endocrinologists be they gynaecologist or endocrinologist.

Diana Hamilton-Fairley

Taking it Lying Down Sexually and Teenage Motherhood by Frances Hudson & Bernard Ineichen. Macmillan, 1991, 243 pages, with figures and tables, £30.00

Teenage girls who become pregnant and continue their pregnancies tend to come from families where teenage pregnancy is common and in which the teenager herself has failed to achieve, often through lack of adequate parenting and poor education. The pregnancy gives her status and a purpose in life for almost the first time but the stresses of motherhood often result in sub-optimal care of the child because of her lack of maturity and scanty resources. Frances Hudson is the head-teacher of a unit for schoolgirl mothers in Bristol and Bernard Ineichen is a lecturer in community medicine. They have a large experience of helping these girls and present a vivid and full picture of the teenage mother and her life. Anyone who has worked with these girls will recognize the accuracy of their descriptions — they provide the reader with concentrated experience that would be very valuable to someone new to this field. Their review of published material is scholarly and comprehensive.

They point out that, in principle, society gives teenagers a choice of abortion and continuing the pregnancy but that those who continue often experience hardship because they obtain much less support than they need from their families and from the state. They stress that these girls are caught in a trap set by the poor quality of their home life and schooling and then by lack of income and poor housing. Their sex education has not been sufficient to give them the ability to establish standards, or to plan this aspect of their lives. Intercourse can be a defiant gesture towards their parents and often seems the inevitable price for a relationship with a man.

The authors have a much more limited experience of teenagers who chose abortion and some of their comments suggest that they do not consider abortion a satisfactory management for unwanted pregnancy. Those with a large experience of the 40 per cent of pregnant teenagers who decide on abortion know that these girls tend to be different from those who choose to be or who are resigned to being mothers. Those who select abortion tend to have benefited more from their upbringing. They have plans for their lives and try not to be the victims of circumstance. The authors clearly know this and accept that abortion is an option but this aspect of the book is much less developed. The girls they describe really are the ones who are 'taking it lying down'.

David Paintin

Cytopathology of the Uterine Cervix, by Alexander Meisels and Carol Morin. Published by the American Society of Clinical Pathologists and distributed outside the US and Canada by Raven Press, New York, NY 10036, 351 pages fully illustrated, $170

This is much more than an atlas of cytopathology. The authors have addressed many of the controversial issues in cytology. The related topics of colposcopy and management of cervical intraepithelial neoplasia, carcinogenesis and the possible role of the human papilloma virus are explored in detail.

It is a useful reference volume but the excellent illustrations and the large chapter on technical considerations also make it a workshop manual which is likely to spend as much time on the bench as on the shelf.

This Canadian production is unequivically North American in its approach and some aspects, such as the Bethesda system, have not been adopted in the United Kingdom. Nevertheless, cytotechnologists and cytopathologists will undoubtedly find this book interesting and educational.

Ian Duncan

Baillière's Clinical Rheumatology International Practice and Research. Pregnancy and the Rheumatic Diseases, Vol. 4, No. 1, April 1990, edited by A. L. Parke. Baillière Tindall, London, Philadelphia, 1990, 1–176 with figures and tables UK annual subscription £41.00, Single issue £22.50

This is an outstanding but useful volume bringing together, as it does, experts both in the clinical and basic aspects of the rheumatic diseases in pregnancy.

As rheumatology deals more and more with younger patients throughout the world, and numbers of those with lupus and overlap diseases seem to be increasing annually, so the clinically difficult decisions of management of these diseases in pregnancy becomes more important—indeed, in centres throughout the world there are now specific combined pregnancy clinics dealing with these diseases on a weekly basis.

Particularly outstanding are the chapters on sex hormones and the immune system by Dr Robert Lahita, who has contributed so much to this field, and by Dr Nigel Harris who has written a timely and comprehensive review of the antiphospholipid syndrome in pregnancy. Excellent chapters by clinicians who have vast experience of their own particular rheumatic diseases in pregnancy are W. F. Kean and Watson Buchanan (rheumatoid), Jill Buyon (lupus) and Carol Black (scleroderma), as well as an up-to-date review of anti-rheumatic drugs in pregnancy by Drs P. Brooks and C. J. Neads.

This volume is a credit to Dr Ann Parke who herself has been in the forefront of combined rheumatic disease-obstetric clinics.

G. R. V. Hughes

The BBC Pregnancy and Post Natal Exercise Video with Rosemary Conley & Jane Ashton. BBCV 4639, £10.20 (90 mins duration)

Today's emphasis on physical fitness and health has led to an upsurge in requests for advice on exercise in pregnancy from sport and aerobics to gym workouts. Certainly most women wish to regain their figures as soon as possible postpartum.

The BBC Video of Antenatal and Postnatal exercises offers a range of exercises for the childbearing year. The programme has been written and designed by two experienced obstetric physiotherapists, Jane Ashton and Margie Polden. Rosemary Conley, who has already released the successful Whole Body Programme BBC video, introduces the exercises and her encouragement throughout keeps up the momentum.

The video is split up into sections. Normal physical changes and obstetric complications which might preclude women from some exercises are discussed briefly in the introduction by midwife and obstetrician. Safety aspects of exercise are stressed and reinforced throughout the programme.

The antenatal section is demonstrated by Jane Ashton at 37 weeks pregnancy who demonstrates good posture, backcare, and pelvic floor exercises excellently. Followed by a warm up, stretches, floor exercises and an all important relaxation technique.

The postnatal programme progresses from gentle to stronger exercises, graduated from birth to 4 months. All are realistically devised to include the new baby. Rosemary Conley then demonstrates stronger maintenance exercises to continue once the body has returned to normal.

On first viewing, the programme appears to be taken rather fast and, at first some exercises are difficult to perform to the accompanying music. However, with practice, by keeping the introductory advice in mind, one can catch up.

Apart from a few personal reservations overall this is an excellent video for women during the childbearing year.

Lizzie Hibbitt

Books received some of which may be reviewed at a later date

Lasers in Gynaecology (Vol. 4 in the series Lasers in Medicine and Surgery) edited by Chris Sutton. Chapman & Hall Medical, London, New York, 1991, 274 pages, with figures, tables and plates, £40.00

Haemostasis and Thrombosis in Obstetrics and Gynaecology edited by I. A. Greer, A. G. G. Turpie & C. D. Forbes. Chapman & Hall Medical, London, 1991, 573 pages, with figures and tables, £65.00

Obstetrics. Normal & Problem Pregnancies Second edition, edited by Steven G. Gabbe, Jennifer R. Niebyl & Jo Leigh Simpson, Churchill Livingstone, New York, Edinburgh, 1991, 1376 pages, 461 illustrations, £65.00

Women's Health Matters edited by Helen Roberts Routledge, London and New York 1992, 200 pages, £10.99

Health After Childbirth by C. MacArthur, M. Lewis & E. G. Knox. Published for the University of Birmingham by HMSO London, 1991, 304 pages, £22.50

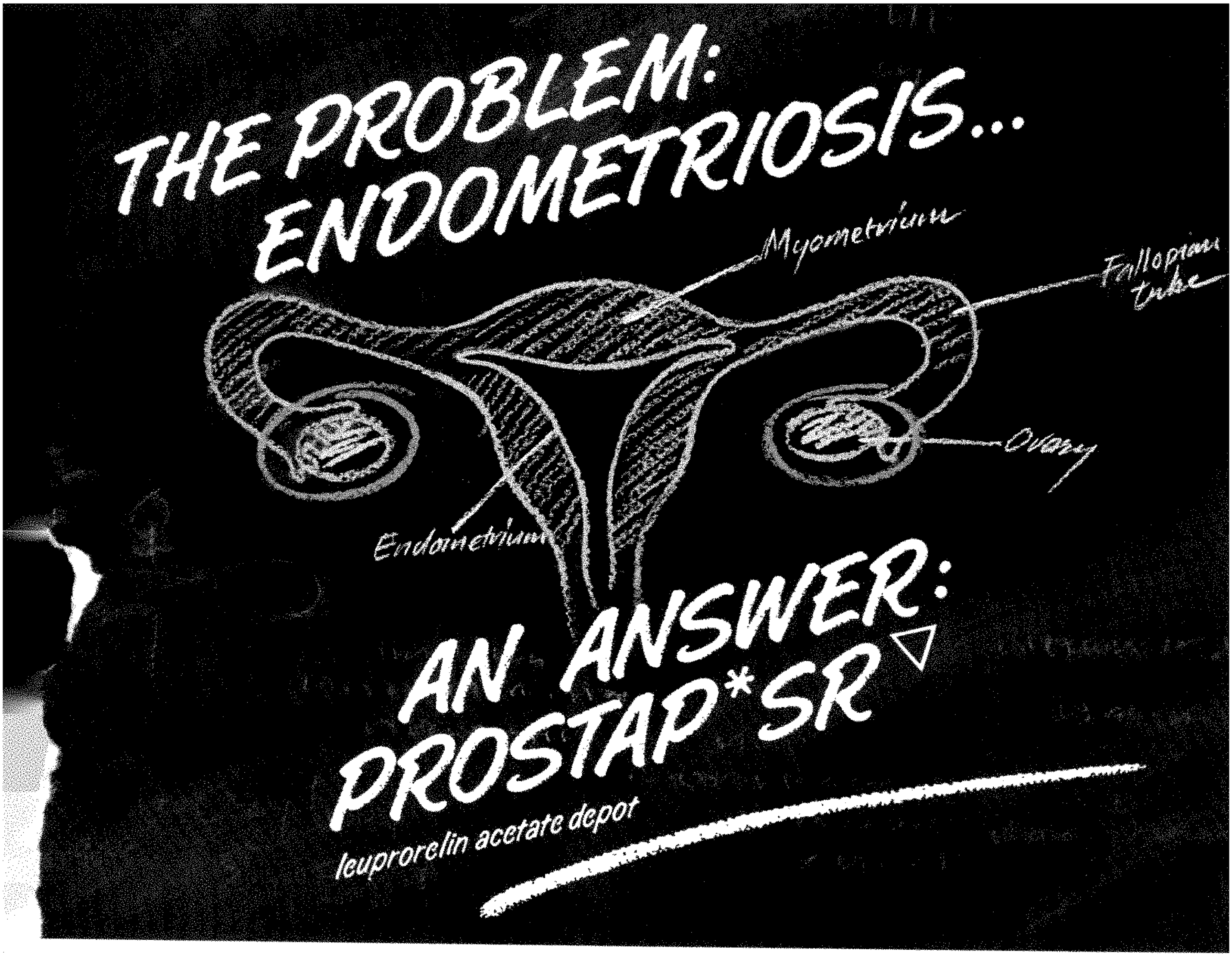
Year Book of Obstetrics and Gynecology 1991 edited by Daniel R Mishell, Thomas H. Kirschbaum & C. Paul Morrow. Mosby Year Book, St Louis Baltimore, London, 1991, 570 pages, £57.95

Oxford Reviews of Reproductive Biology Vol 13 edited by S. R. Milligan. Oxford University Press, Oxford, New York, Tokyo, 311 pages with figures and tables, £45.00

Proceedings and Symposiums

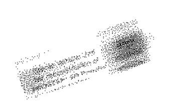
Oral Contraceptives & Breast Cancer Report of the Committee on the Relationship Between Oral Contraceptives and Breast Cancer. Published for the Institute of Medicine by the National Academy Press, Washington DC, 1991, 185 pages, £21.50

MIRIAD. Midwifery Research Database 1991 Report Published by the National Perinatal Epidemiology Unit, Radcliffe Infirmary, Oxford. Copies available from the Royal College of Midwives, 15 Mansfield St, London W1M 0BE, 205 pages, £5+50p postage



Effective GnRH agonist therapy for endometriosis,[1,2] from a simple monthly subcutaneous injection.

A very fine suspension, given through a fine gauge needle, offers patient acceptability and ease of administration in clinic, outpatient or domiciliary use.



PROSTAP* SR ▼

leuprorelin acetate depot

A Logical Approach to Endometriosis

ERENCES
lugi AM *et al* Fertility & Sterility 1990; **54** (3) 419-427. (RJG33) **2.** Adashi E *et al.* Data on File, Lederle Laboratories.
BREVIATED PRESCRIBING INFORMATION Before prescribing Prostap SR, please refer to full data sheet.
sentation: Vials containing 3.75mg leuprorelin acetate as microcapsule powder. For reconstitution with Sterile Vehicle, presented in a prefilled syringe. **Indications:** The
agement of endometriosis, including pain relief and reduction of endometriotic lesions. **Dosage:** 3.75mg administered as a single subcutaneous or intramuscular injection every
th for a maximum period of 6 months. Treatment should be initiated during the first 5 days of the menstrual cycle. **Contraindications:** Lactation, pregnancy, undiagnosed
rmal vaginal bleeding. **Warnings:** Whilst ovulation is usually inhibited during therapy, contraception is not ensured, therefore, patients should use non-hormonal methods of
aception. During the early phase of therapy, sex steroids temporarily rise, possibly leading to an increase in symptoms. This, however, dissipates with continued therapy.
utions, side-effects: The induced hypo-oestrogenic state results in a small loss in bone density over the course of treatment, some of which may not be reversible. However,
one six-month treatment period, this bone loss should not be important. The generally accepted level of bone loss with LHRH analogues such as Prostap is 5%. For patients
ajor risk factors for decreased bone mineral content, Prostap therapy may pose an additional risk. Other side effects reported are mainly those related to hypo-oestrogenism;
hes, headaches, emotional lability, and vaginal dryness. **Legal category:** POM. **Package Quantities:** Vials containing 3.75mg leuprorelin acetate as microcapsule powder.
d syringes containing 2ml of sterile vehicle. **Basic NHS cost:** £125.40. **Product Licence Numbers:** Prostap SR Powder 3.75mg vials; PL0095/0218. Sterile vehicle prefilled
ges PL0095/0220. Cyanamid of Great Britain.
urther information, see data sheet.
erle Laboratories, Fareham Road, Gosport, Hants PO13 0AS.
(0329) 224000

***Trademark of Takeda**
***Under licence of Takeda Chemical Industries Ltd, Japan.**
Date of Preparation of API: December 1991.

British Journal of Obstetrics and Gynaecology

Volume 99 No 3 March 1992

CONTENTS

Commentaries

Audit in gynaecology 175
G. Chamberlain

Aetiology of cerebral palsy 176
B. Lamb & R. Lang

Therapeutic uses of transcervical catheterization of the fallopian tubes 178
R. G. Forman & M. G. Chapman

Role of the senior house officer in the labour ward 180
J. R. Pogmore

Obstetrics

Objective measurement of anxiety in hypertensive pregnant women managed in hospital and in the community 182
W. Cartwright, K. J. Dalton, H. Swindells, S. Rushant & P. Mooney

The accuracy of catheter-tip pressure transducers for the measurement of intrauterine pressure in labour 186
S. Chua, S. Arulkumaran, M. Yang, S. S. Ratnam & P. J. Steer

Prenatal microbiological risk factors associated with preterm birth 190
H. M. McDonald, P. Jolly, J. A. O'Loughlin, R. Vigneswaran & P. J. McDonald

Can out-of-hours work by junior doctors in obstetrics be reduced? 197
M. McKee, P. Priest, M. Ginzler & N. Black

Determinants of caesarean section rates in Italy 203
F. Parazzini, N. Pirotta, C. La Vecchia & L. Fedele

Serum and intracellular magnesium during normal pregnancy and in patients with pre-eclampsia 207
J. Seydoux, E. Girardin, L. Paunier & F. Beguin

Fetal and Neonatal Medicine

The effects of fetal exposure to danazol 212
P. J. Brunskill

A tale of two prior probabilities—avoiding the false positive antenatal diagnosis of autosomal recessive polycystic kidney disease 216
R. J. Lilford, H. C. Irving & E. B. Allibone

Screening for congenital heart disease prenatally. Results of a 2½-year study in the South East Thames Region 220
G. K. Sharland & L. D. Allan

Gynaecology

The multidisciplinary management of a family with epithelial ovarian cancer 226
D. J. Cruickshank, N. Haites, S. Anderson, H. Matheson, M. H. Hall, B. Milner, A. Ah-See, I. Gunn, O. Eremin, F. Gilbert & A. W. Johnston

Which hormone tests for the diagnosis of polycystic ovary syndrome? 232
S. Robinson, D. A. Rodin, A. Deacon, M. J. Wheeler & R. N. Clayton

Fertility Control

Oral contraceptive use and breast cancer risk: a meta-analysis of variations with age at diagnosis, parity and total duration of oral contraceptive use 239
L. Rushton & D. R. Jones

Reproductive Science

Renal sodium retention does not occur during the luteal phase of the menstrual cycle in normal women 247
D. L. Bisson, G. D. Dunster, J. P. O'Hare, D. Hampton & M. D. Penney

Increased whole blood platelet aggregation in normal pregnancy can be prevented *in vitro* by aspirin and dazmegrel (UK38485) 253
L. A. Norris, B. L. Sheppard & J. Bonnar

Case Reports

Multiple fetal anomalies in the first trimester; detection using transvaginal ultrasound and therapeutic abortion using mifepristone (RU486) in conjunction with gemeprost vaginal pessaries 258
R. C. Henshaw, A. P. M. Smith, N. C. Smith & G. I. Murray

Pregnancy following intravaginal embryo transportation 259
J. D. Critchlow, P. L. Matson, K. Killick & B. A. Lieberman

High-dose immunoglobulin in the antenatal treatment of neonatal alloimmune thrombocytopenia: case report and review 260
K. Marzusch, M. Schmaidt, J. Dietl, E. Wiest, C. Hofstaetter & R. Gölz

Successful twin pregnancy despite proven intraperitoneal chlamydial infection at implantation 263
P. Curtis, N. Amso, R. M. Parnaby, C. C. Kibbler & R. W. Shaw

Short Communications

Immunohistochemistry in pelvic nodes of patients with cervical cancer 265
G. Gitsch, A. Reinthaller, P. Kohlberger, G. Tatra & G. Breitenecker

A comparison of two endometrical samplers 266
A. L. Sheehan, M. D. Read & B. W. Codling

Blair Bell Research Society 268

Correspondence 271

Book Reviews 273

Erratum The article on p. 132 in the February contents list should have read:
External ocular trauma in instrumental and normal deliveries 132
R. Holden, D. G. Morsman, G. M. Davidek, G. M. O'Connor, E. C. Coles & A. J. Dawson

Blackwell Scientific Publications
OXFORD · LONDON · EDINBURGH · BOSTON · MELBOURNE · PARIS · BERLIN · VIENNA
Printed in Great Britain by Headley Brothers Ltd The Invicta Press Ashford Kent and London